Epidemiology

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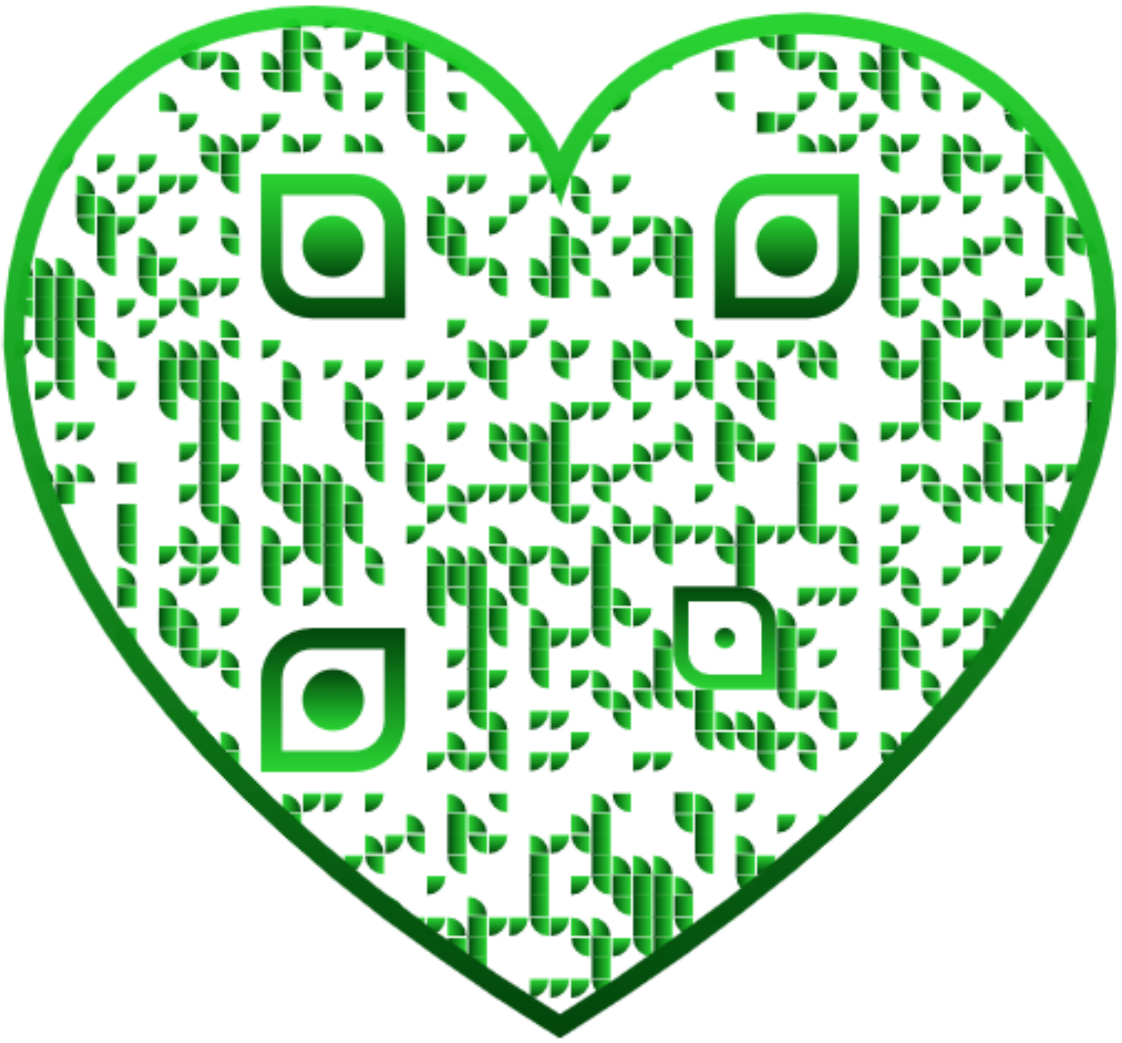

Health Core Sciences

Epidemiology

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Epidemiology

EPI	DEMO	LOGOS
Upon , on ,befall	People , population, man	the Study of

The study of anything that happens to people

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Simple Old Definitions

Oxford English Dictionary

The branch of medical science which treats epidemics

Kuller LH: American J of Epidemiology 1991;134:1051

- ✓ Epidemiology is the study of "epidemics" and their prevention

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Epidemiology is the method used to find the causes of health outcomes and diseases in populations.
In epidemiology, the patient is the community and individuals are viewed collectively.

By definition, epidemiology is the study (scientific, systematic, and data-driven) of the distribution (frequency, pattern) and determinants (causes, risk factors) of health-related states and events (not just diseases) in specified populations (neighborhood, school, city, state, country, global).

It is also the application of this study to the control of health problems

(Source: *Principles of Epidemiology, 3rd Edition*).

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II. EPIDEMIOLOGY

"Is a science which studies the distribution and determinants of health and health related events in populations, and the application of this knowledge for the promotion of health, prevention and control of diseases."

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Modern Definition

- Epidemiology **is the study of the distribution and determinants of health-related states or events in specified populations, and** the **application** of this study to the control of health problems.

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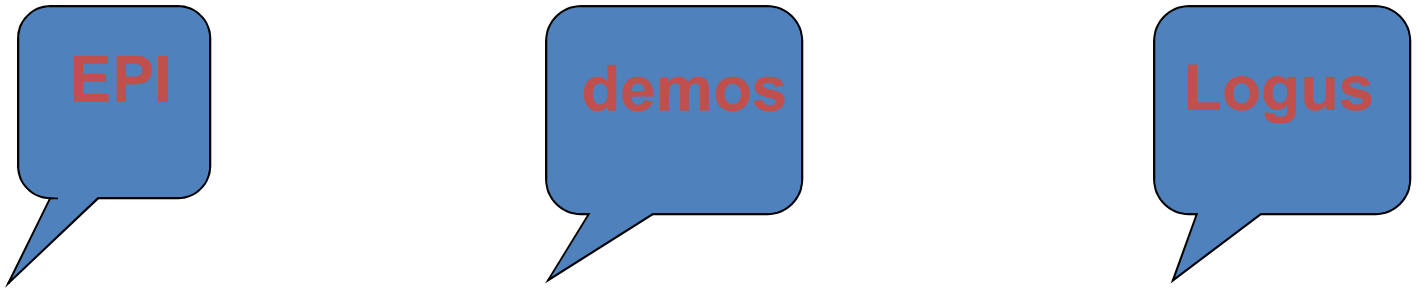
1. DEFINITION OF EPIDEMIOLOGY

- **Originated from three Greek words.**



on, up on **People** **doctrine, study**

- **The term epidemiology was originally applied to the study of *acute infectious diseases* and was defined as:**

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Definition Cont....

- **“*the science of epidemics.”***
- **“The study of the distribution and dynamics of disease in the human population.”**
- **“The study of the distribution and determinants of health related phenomena in the human population.”**

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Current definition

"The study of the *frequency*, *distribution* and *determinants* of *diseases and other health related problems* in human population and the *application* of this to the prevention and control of health problems."

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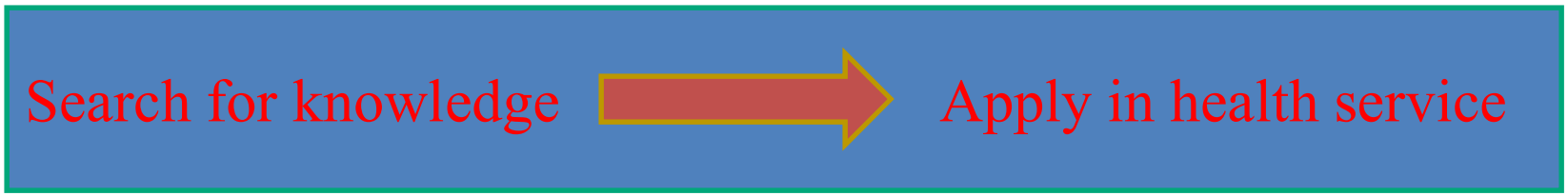
A Modern Definition

- "The study of the distribution and determinants of health-related states in specified populations, and the application of this study to control health problems."

(Last J)



Objectives of Epidemiology

1. To describe the **distribution** and magnitude of health and disease problems in the population.
2. To identify the **etiological factors** – risk factors in the population.
3. To provide the **data** essential to planning, implementation and evaluation of services for prevention, control and treatment of disease and to setting up of priorities for these services.

The ultimate aim of epidemiology is

- to **eliminate or reduce health problem** or its consequences

and

- to **promote health** and well-being of society as a whole.

Purposes of Epidemiology

1. To investigate nature / extent of health-related phenomena in the community / identify priorities
2. To study natural history and prognosis of health-related problems
3. To identify causes and risk factors
4. To recommend / assist in application of / evaluate best interventions (preventive and therapeutic measures)
5. To provide foundation for public policy

Component:

Disease Frequency- Rate and Ratio e.g

Rate- incidence rate, prevalence rate etc

Ratio- sex ratio, doctor-population ratio

Distribution of Disease-

Disease in community → find causative factor

↓

Generate hypothesis

↓

Descriptive epidimiology

Terms taken from the definition

1. ***Frequency:*** **It is a quantitative science**

(it measures frequency of occurrence)

- **It assesses occurrence of a diseases in numbers**

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EPIDEMIOLOGY CONT…

=> Key words in the definition are:

1. **Distribution=> who? Where? And when?**

Of occurrence of health and health related events

2. **Determinants=> factor which may be event, characteristic or any definable entity that brings about change in health and health related conditions.**

It refers to "why diseases occur in certain places? In a certain period? Or in a certain population groups?"

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Cont…

2. Distribution – *is the occurrence of diseases and other health problems in terms of* person, place *and* time.

- ***This attempts to answer***

  <u>Who</u>*?* <u>Where</u>*? and* <u>When?</u>

  of disease occurrence.

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Cont…

3. ***Determinants*** **– are factors that are related with the occurrence of a disease in individuals,**

- **It is about causative factors for the occurrence of a disease.**
- **It attempts to answer questions like How? and why? disease occurs?**

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Epidemiology: Definition

Greek words

- Epi – "on or "upon
- demos – the population
- logos – the study of

- **Epi + demos + logos → → →**
  → a study "that which befalls Man"

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‘Study’

- ✓ **It is a scientific discipline which has its** own **foundation, sound methods of scientific inquiry**
- ✓ **it is the basic science of public health.**

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Epidemiology: Definition

- "The study of the distribution and determinants of health related states or events in specified populations and the application of this study to the control of health problems".

(Last 1988)

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Epidemiology: Definition

- **Distribution** is concerned with:

→ **Pattern & frequency** of health events in a population

- **Pattern** refers to: the occurrence of health-related events by time, place and person characteristics.

- **Frequency** refers to measurement of frequency of health-related events(disease disability or death) and summarizing this information in the form of rates and ratios.

Descriptive Epidemiology

What ? health-related states or events

Who ? → person

When ? → time

Where ? → place

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Definition…

6. ***Application:*** *to the prevention and control of health problems*

EPIDEMIOLOGY PROVIDES INFORMATION FOR ACTION

- It is applied science, i.e direct practical applications.
- The aim of all about frequency, distribution of diseases is to identify effective prevention and control strategies.

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EPIDEMIOLOGY CONT…

3. **Health and health related events** => **epidemiology is concerned not only with disease but events like birth, death, migration e.t.c.**

The central concern of epidemiology is promotion and maintenance of health through the prevention of diseases.

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EPIDEMIOLOGY CONT…

4. **Human population => though epidemiology is concerned with population, there is strong interrelation with clinical medicine.**

5. **Application- epidemiology is an applied science.**

   - **The ultimate purpose of all epidemiological studies is the prevention and control of health problems.**

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Single Overriding Objective:

Everything we do must directly improve the health of the people!

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Present Perspective of EPI:

- A philosophical study of health problems;
- An art of the possible;
- A science with wider application.

(*Oxford Text Book of Public Health*)

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Epidemiology: Philosophical study of health problems…

- Human disease does not occur at random.
- Human disease has causal factors.
- These causal factors can be identified through systematic investigation of populations.
- Human disease can be prevented (have preventive factors).
- Disease can not be attributed to operation of one factor.

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Epidemiology: Art of epidemiology…

Skills of appropriateness, creativity and innovation are essentia

- Exact observation

- Correct interpretation

- Rationale explanation

- Scientific construction

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Epidemiology: A Science

- It follows all basic tenets of science;
- It has an order and definitive purpose;
- It is systematic and has sequence, relevance and inference;
- It follows ethics;
- It has wider and acceptable application.

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Who is an Epidemiologist?

- Any person who researches into occurrence of disease or disability in groups of people.

- Qualifications of an Epidemiologist:
  - Familiar with statistical techniques
  - Well grounded in diagnosis of disease
  - Thorough with medicine, relating to epidemics
  - Good knowledge of bacteriology, immunology and physiology
  - Knowledge of principles of preventive

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Objectives of Epidemiology:

- Establishing the determinants/causation of disease
- Elucidation of the natural history of disease & prognosis of disease.
- Description of the health status of the population
- Evaluating interventions and health service provision
- Planning health services & decision making in clinical medicine.

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Epidemiological sequence and purpose:

- Identify disease/health problem
- Linking with cause/risk factors
- Establishing causal relationship
- Designing an intervention for controlling health problem
- Evaluating effectiveness of intervention

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Scope of Epidemiology:

- Originally, Epidemiology was concerned with **Epidemics of communicable diseases & epidemic investigations.**

  "***the science of epidemics.***"

- Later extended in to **endemic communicable diseases and non-communicable diseases.**

- NB: At present epidemiology can be applied to all disease conditions and other health related events

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Major Approaches in Epidemiology:

1. Descriptive Epidemiology:

- Concerned with describing the frequency and distribution of diseases and other health related conditions by time, place, and person.

Major characteristics in Descriptive Epidemiology:

- Person, place and time.
- To describe the occurrence of a disease fully, the following questions must be answered.
  - Who is affected?
  - Where?
  - When do the cases occur?
  - How many?

- USED TO GENERATE HYPOTHESIS

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Major Approaches in Epidemiology…

2. Analytic Epidemiology:

- Involves explicit comparison of groups of individuals to identify determinants of health and diseases.

  - It asks the question:
    - –Why?
    - –How?

- USED TO TEST HYPOTHESIS

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EPIDEMIOLOGY HAS THE METHODOLOGY TO:

- **Determine the extent of disease in the community**
- **Study the natural history and prognosis of disease**
- **Identify associations and potential etiology (causes) of a disease and risk factors for disease**
- **Evaluate new preventive and therapeutic measures and new modes of health care delivery**

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Health-related states or events

Epidemics of communicable diseases.

Endemic communicable diseases and non communicable diseases

Chronic diseases, injuries, birth defects, maternal-child health, occupational health, and environmental health

Behaviors related to health and well-being

- **Hence, Health-related states or events refers to any diseases, causes of death, behaviors such as use of tobacco, positive health states, reactions to preventive regimes and provision and use of health services ,etc…**
- Factor that can affect the health of individual positively and negatively.

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Cont…

4. Disease and Health-related problems

It includes – both diseases and physiological and/or psychological dysfunction of the body

It also includes other health related problems like:

- **Vital events, births, deaths, marriage, divorces etc**
- **Health related behaviour – sexual behaviour, smoking, alcoholism, drug abuses**
- **Social factors, such as poverty.**

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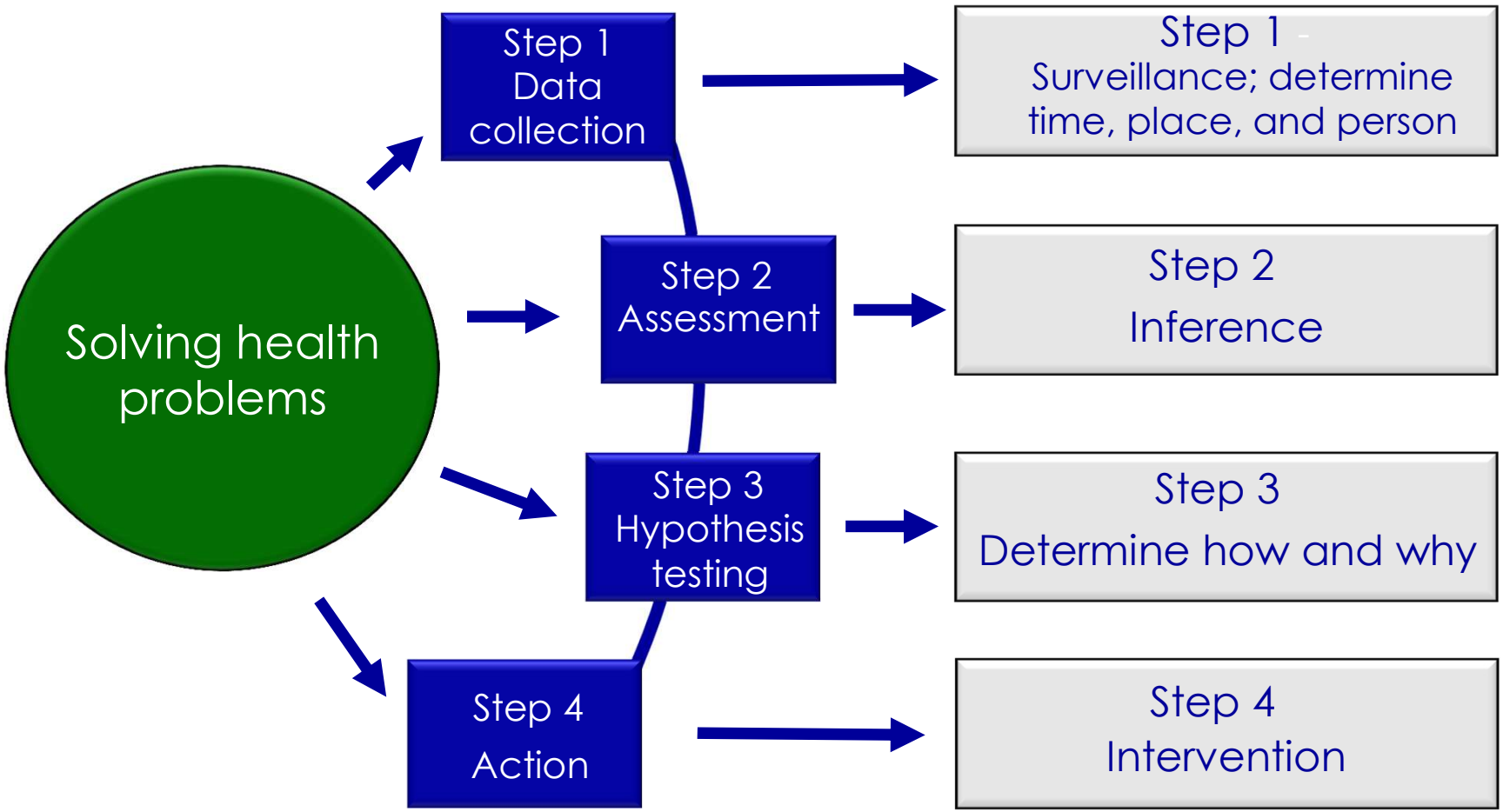
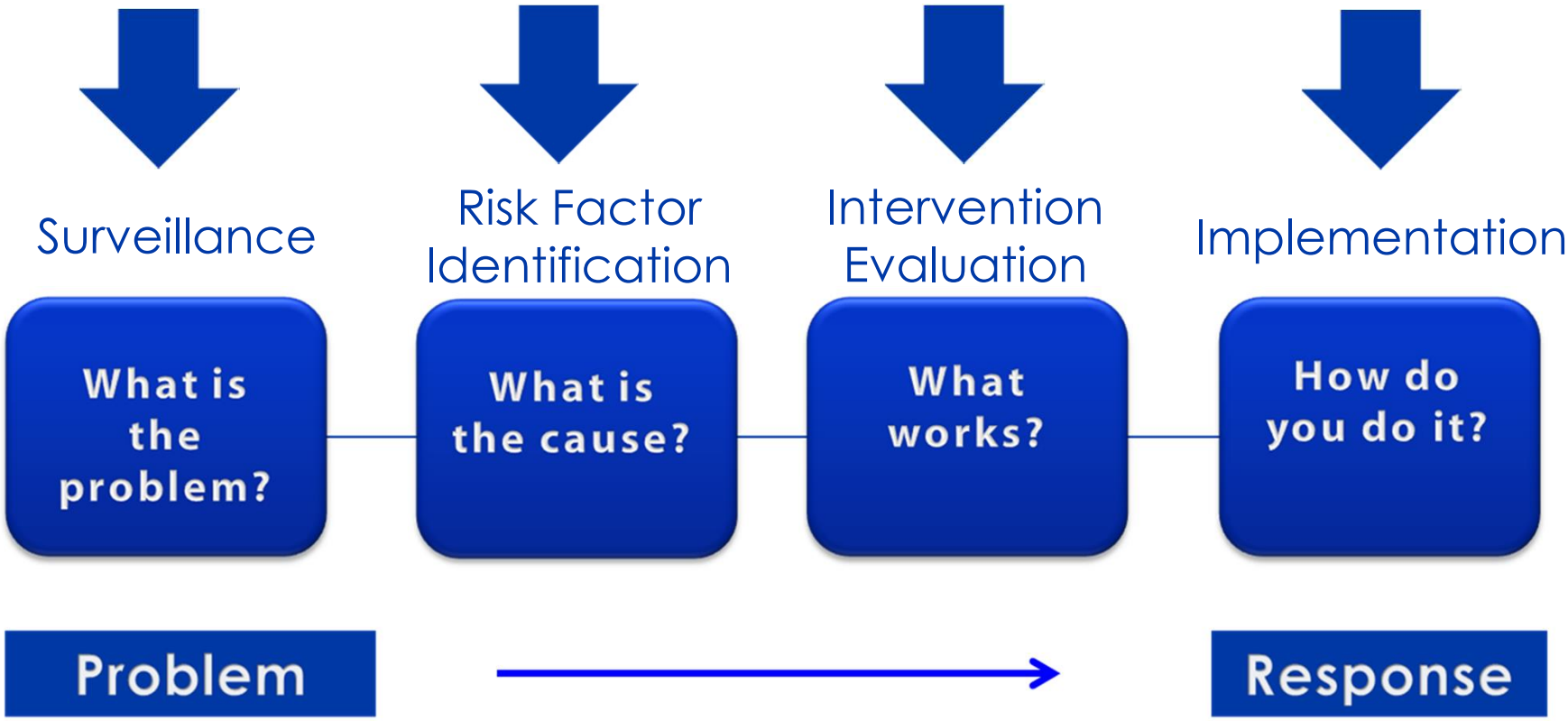
Solving Health Problems


Solving health problems
Step 1 Data collection
Step 2 Assessment
Step 3 Hypothesis testing
Step 4 Action
Step 1 - Surveillance; determine time, place, and person
Step 2 Inference
Step 3 Determine how and why
Step 4 Intervention

A Public Health Approach



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Public Health

~Vision~

Healthy People in Healthy Communities

~Mission~

Promote physical and mental health

and

Prevent disease, injury, disability

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Public Health…

- Prevents epidemics and the spread of disease

- Protects against environmental hazards

- Responds to disasters and assists communities in recovery

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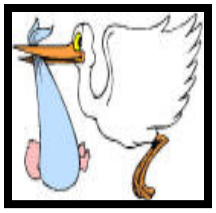
Public Health…

- Prevents injuries

- Promotes healthy behaviors



- Assures the quality and accessibility of health services

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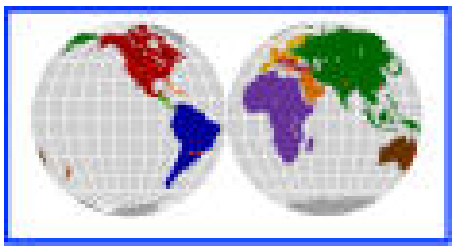
10 Essential Services

3. **Inform, educate, and empower people about health issues**

4. **Mobilize community partnerships to identify and solve health problems**



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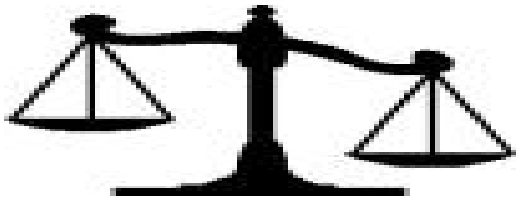
10 Essential Services

5. **Develop policies and plans that support health efforts**

6. **Enforce laws and regulations that protect health and ensure safety**



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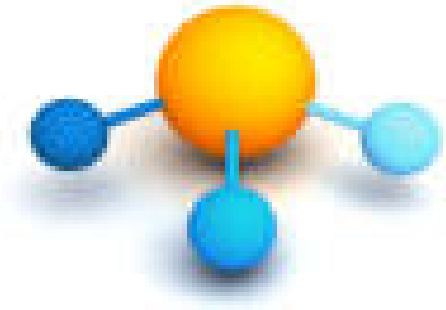
10 Essential Services

7. **Link people to personnel health services and assure the provision of health care**



8. **Assure a competent public health and health care workforce**

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10 Essential Services

9. **Evaluate the effectiveness, accessibility, and quality of services**

10. **Research for new insights and innovative solutions to health problems**

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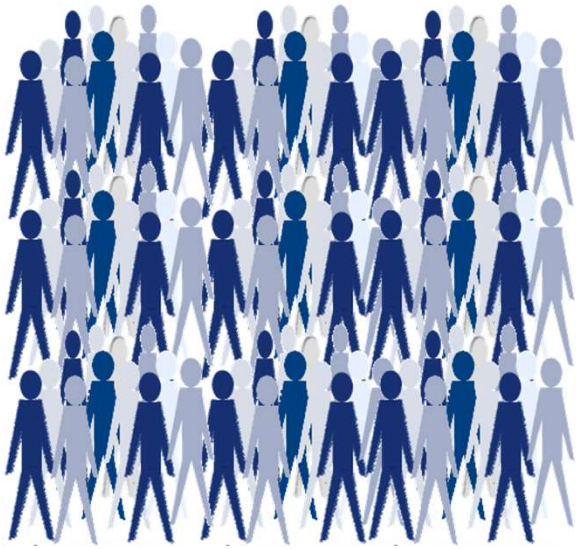
Public Health Approach

Public Health Model

Versus

Medical Model



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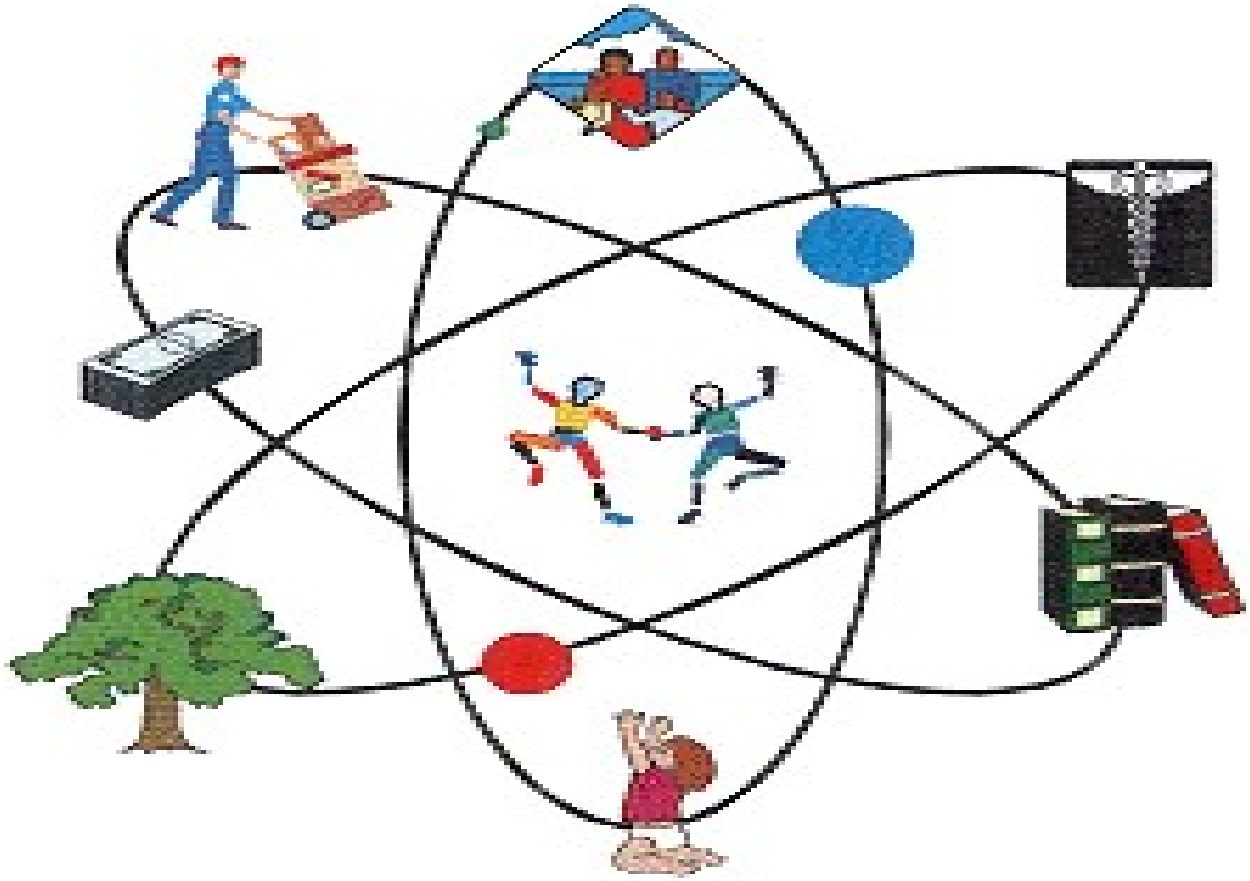
Determinants of Health



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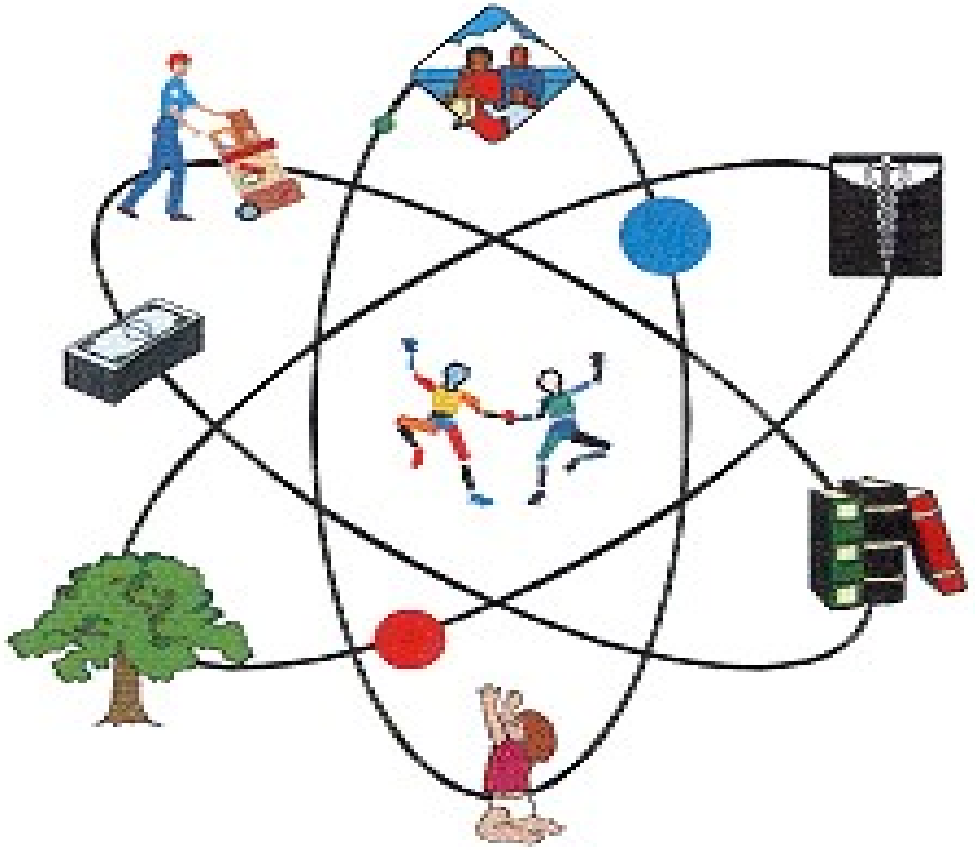
Determinants of Health

- **Genetic**
- **Behavioral**
- **Social**
- **Environmental**
- **Personal health care**



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Achievements

- **Vaccination**
- **Safer Workplaces**

- **Safer & Healthier Food**
- **Motor Vehicle Safety**

Achievements

- **Recognition of Tobacco Use as a Health Hazard**

- **Healthier Mothers and Babies**

- **Fluoridation of Drinking Water**

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Epidemiology Key Terms

epidemic or outbreak: disease occurrence among a population that is in excess of what is expected in a given time and place.

cluster: group of cases in a specific time and place that might be more than expected.

endemic: disease or condition present among a population at all times.

pandemic: a disease or condition that spreads across regions.

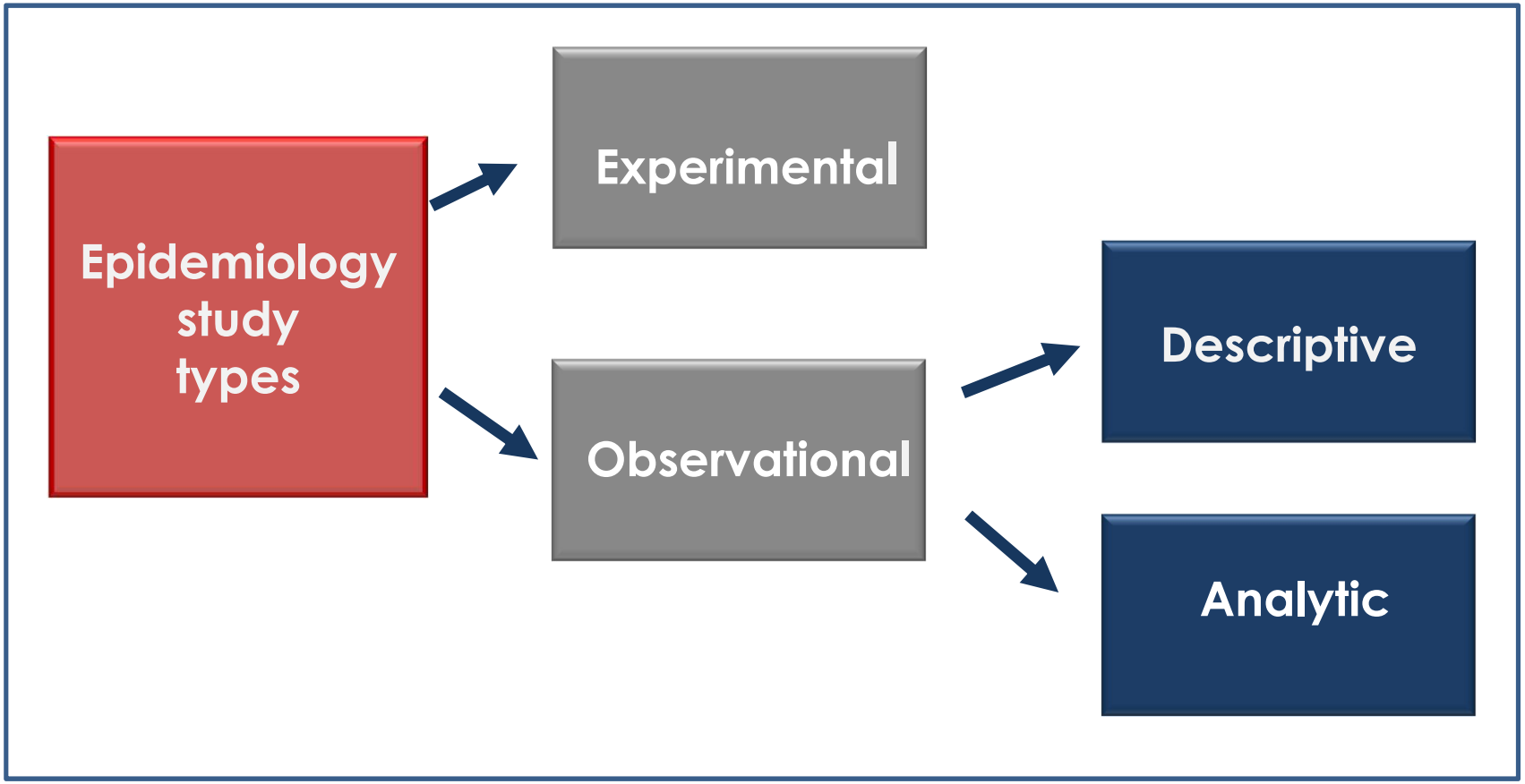
rate: number of cases occurring during a specific period; always dependent on the size of the population during that period.

Endemic: ”Constant presence of a disease or infectious agent within a given geographic area. The usually prevalence of a given disease within such an area.”

Epidemic: “Occurrence in a community or region of cases of an illness or outbreak clearly in excess of expectancy.”

Pandemic: ”Occurring over a wide geographic area and affecting an exceptionally high proportion of the population, i.e. malaria.”

Epidemiology Study Types



Health-related states or events /health problem

- Any communicable, non communicable disease
- Chronic disease
- Any other cause of death ,
- Any bad and healthy behaviors
- Reactions to preventive regimes
- Provision and use of health services
- etc…

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Distribution

- ✓ The frequency and pattern of health related events in a population.
- ✓ **Pattern**
  - ❖ **Time**:-annual occurrence, seasonal occurrence, daily etc.
  - ❖ **Place:-**geographic variation, urban-rural differences, location
  - ❖ **Person:-**age, race, sex, marital status, etc.
- ✓ **Frequency** :- the number , proportion , rate or risk of health related state or events in a specified population

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Determinants

- ✓ **Causes and other factors** that influence the occurrence of health-related state /events
- ✓ Can be **physical, biological, social, cultural, and behavioral** factors
- ✓ Example :
  - ❖ Cigarette smoking –lung cancer
  - ❖ food insecurity -malnutrition
  - ❖ bed net utilization----malaria
  - ❖ condom utilization -----HIV/AIDS

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Specified populations

- **Epidemiology concerned with the collective health of the people in a community or other area**
- **Why we specify the population?**
- In order to be able to compare between two populations
- For example, if we say 50 people in this room have an infection compared with 100 people in the next room, does it mean that infections are less common in this room?

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Application

- ✓ Epidemiology **provides information for public health action.**
- ✓ However, using epidemiologic data is an art as well as a science.
- ✓ **planning how to control and prevent disease in the community.**

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Major categories of epidemiology

- PHARMACOLOGIGALLY

PHARMACOEPIDEMIOLOGY

PUBILICALLY EPIDEMIOLOGY

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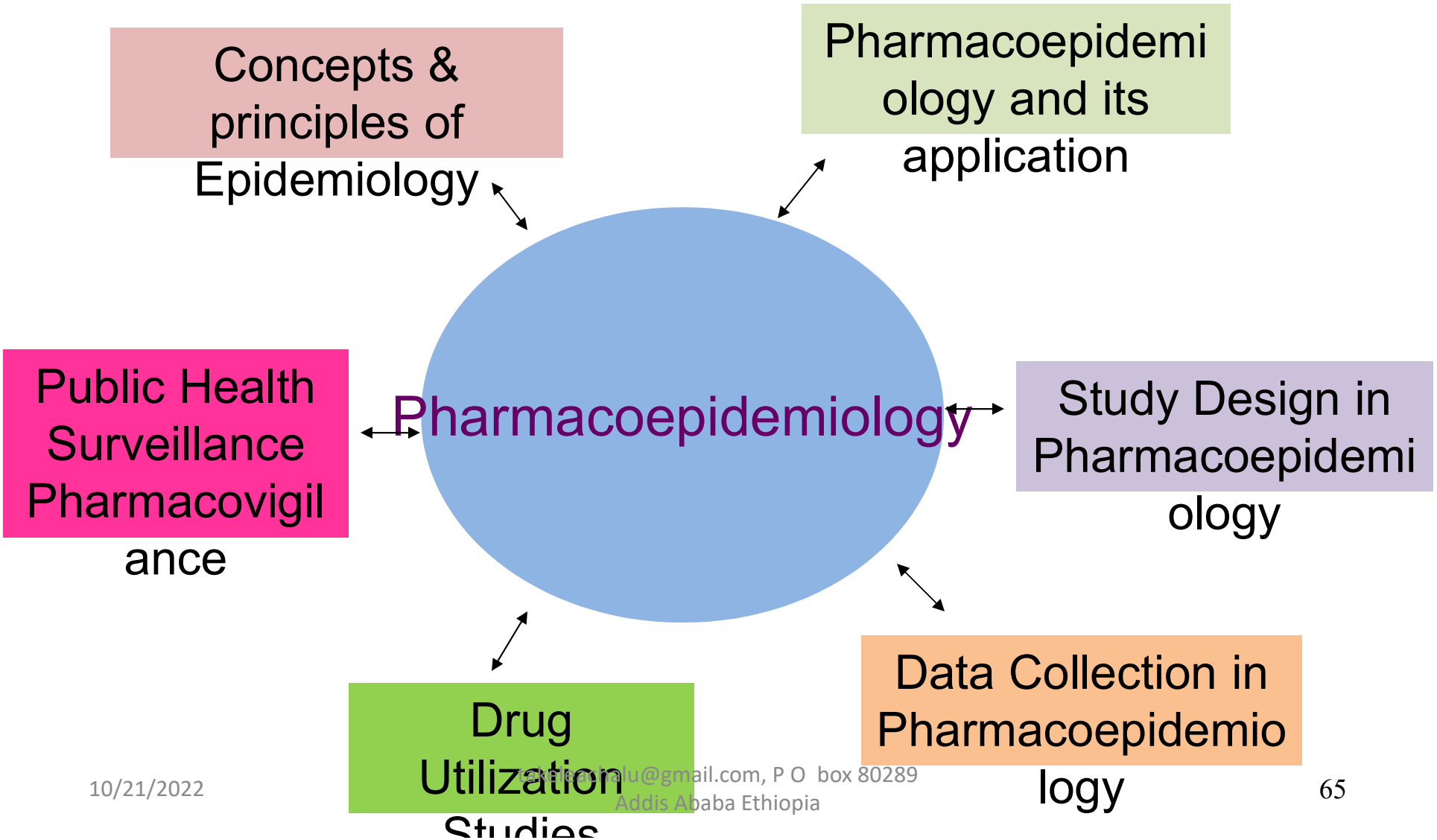
Pharmacoepidemiology



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1.1. Definitions of Pharmacoepidemiology

- **Study of drugs** as **determinants of health and disease** in the general **unselected population**
- **Science** of **measuring drug mediated health events** in well **defined large number of populations**
- Study of the **utilization and effects of drugs in large numbers of people**
- **Application** of **epidemiological methods to pharmacological issues**

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Defin….

- It links **exposure and outcome** for any appropriate sub-groups in any selected medicines in terms of
  - Therapeutic gain
  - Length of life
  - Quality of life
  - Adverse events
- Pharmacoepidemiology **borrows** from both pharmacology and epidemiology
  - a bridge science - **spanning both pharmacology and epidemiology**

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1.2. Historical Background

- **US law, Pure Food and Drug Act,** passed in **1906** followed by **FD and cosmetic Act** in **1938**.
- **Preclinical toxicity testing and clinical data** about drug safety **required before drug marketed.**
- **'Thalidomide disaster' in 1961** led to establishment of **committee of safety of medicines in 1968** in UK and changes elsewhere.
- 'Pharmacoepidemiology' first appeared in medical literature in British Medical Journal (BMJ) in **1984.**

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Drug Toxicity

- Thalidomide
- Chloramphenicol and Grey Baby Syndrome
- Gynecological cancer in offspring of women receiving Diethyl Stilboestrol
- Oculomucocutaneous syndrome with Practolol
- Liver disease from Benoxaprofen
- Valvular heart disease from Dexfenfluramine
- Cardiac arrhythmias with Terfenadine
- Multiple drug interactions with Mibefradil

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1.3. Pharmacoepidemiology Scope and Relationship with other fields

Pharmacoepidemiology Scope

- Pharmacoepidemiology is the application of epidemiological principles and methods to the study of drug effects in human populations.

- The goals are to
  - **characterize, control and predict the effects and uses of pharmacological treatment regimens** in a defined population.

- Pharmacoepidemiology is also concerned with the **economic impact** and **health benefits** of **unintended drug effects.**

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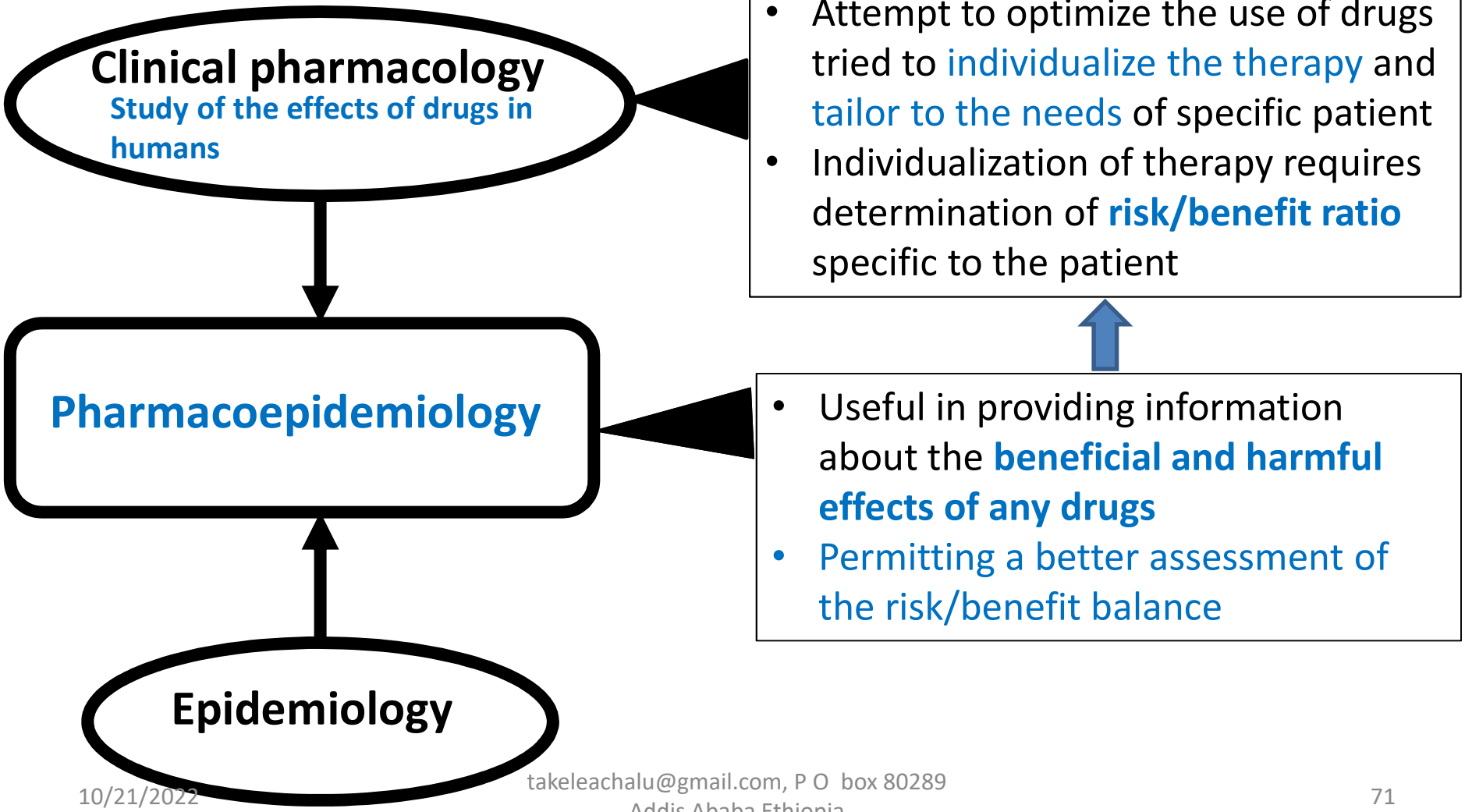
Pharmacoepidemiology vs Other fields


Clinical pharmacology
Study of the effects of drugs in humans
Pharmacoepidemiology
Epidemiology
• Attempt to optimize the use of drugs tried to individualize the therapy and tailor to the needs of specific patient
• Individualization of therapy requires determination of risk/benefit ratio specific to the patient
• Useful in providing information about the beneficial and harmful effects of any drugs
• Permitting a better assessment of the risk/benefit balance

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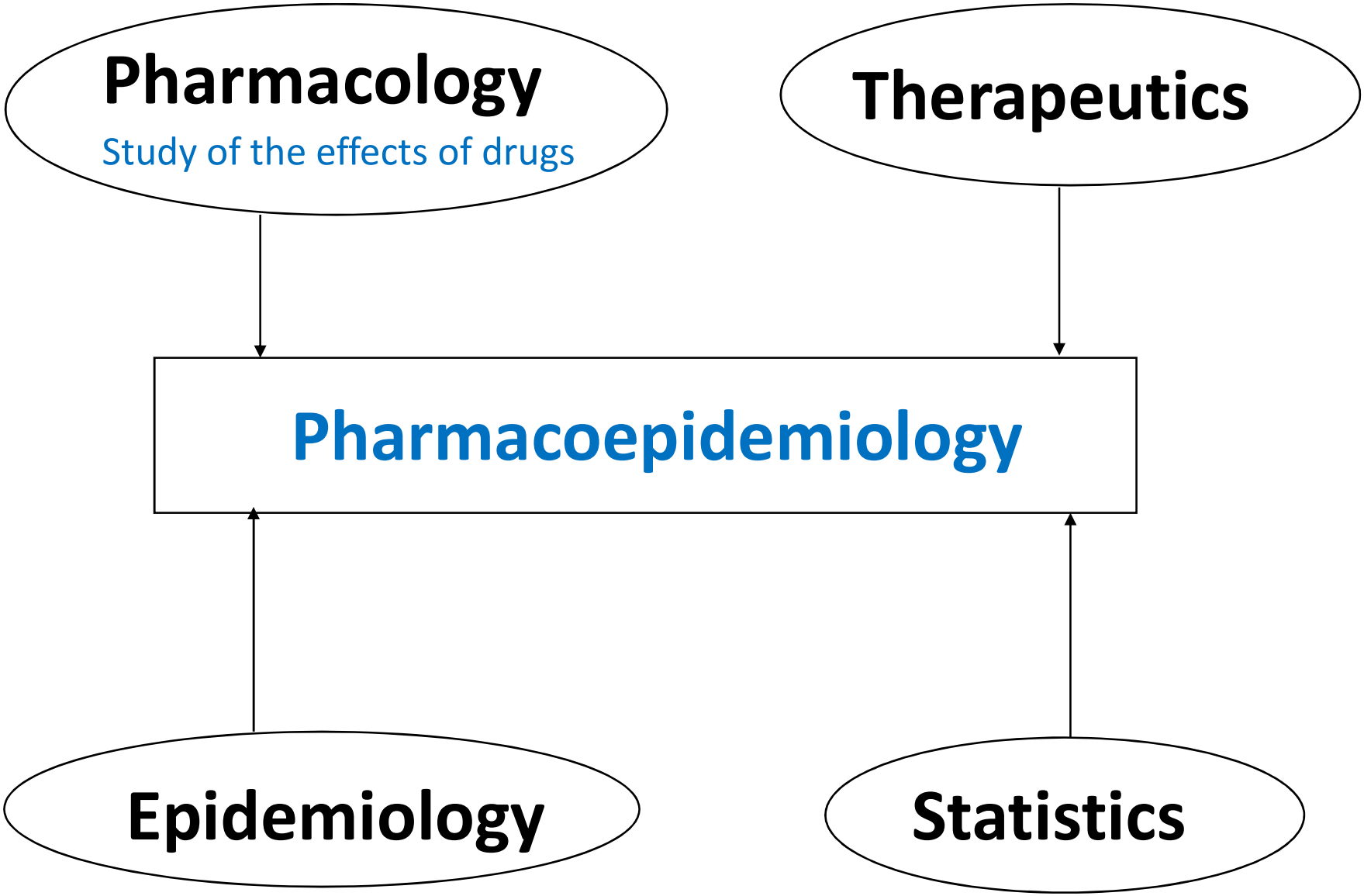

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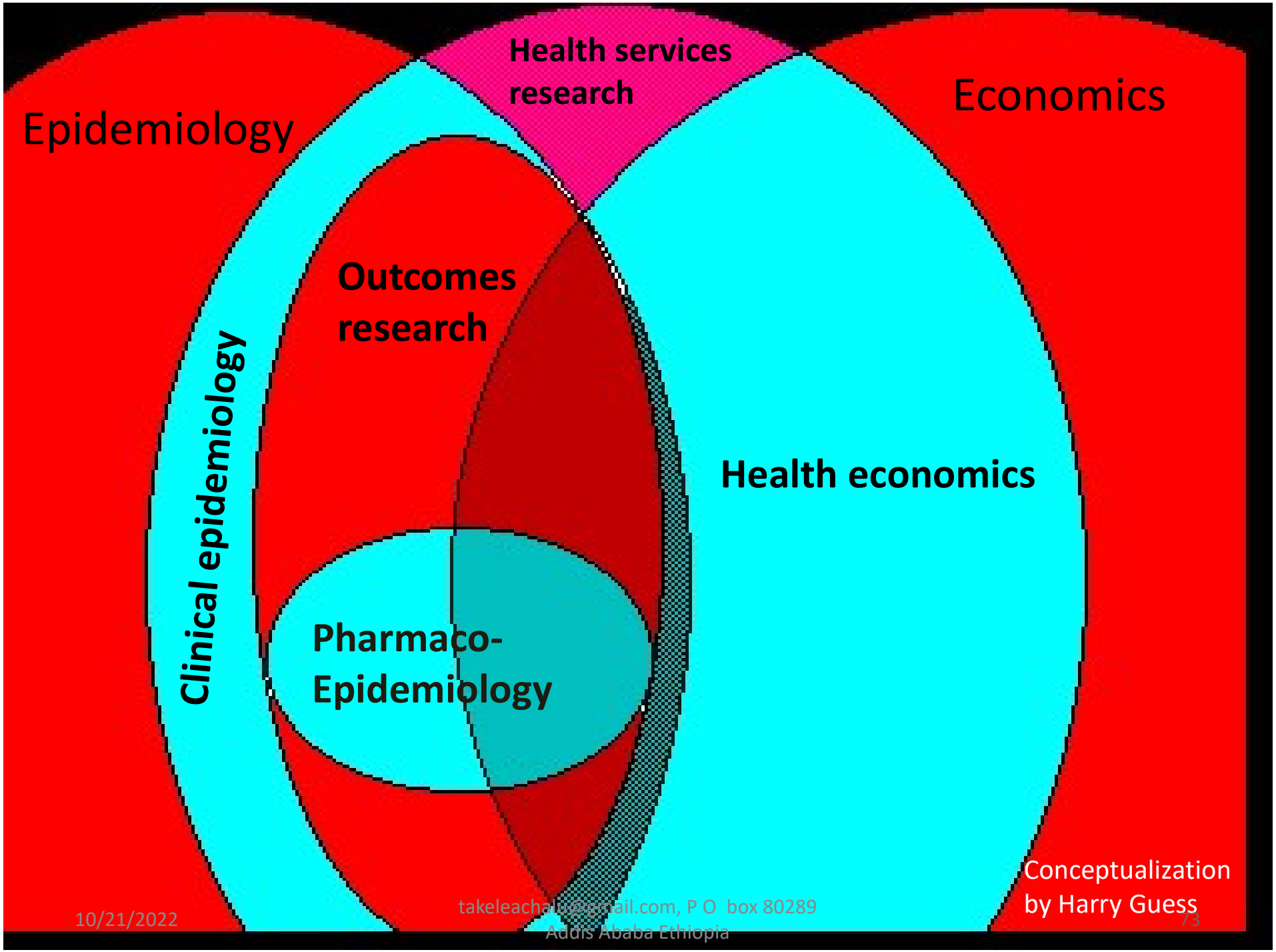

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Major categories of epidemiology

- Epidemiology can be categorized into two:

1. **Descriptive Epidemiology** - Defines the amount and distribution of health problems in relation to person, place and time. It answers the questions ***who, where and when.***
2. **Analytic Epidemiology** – involves explicit comparison of groups of individuals to identify determinants of health and diseases. It answers the questions ***why and how***

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Epidemiology: Definition

- **Distribution** is concerned with:

→ **Pattern & frequency** of health events in a population

- **Pattern** refers to: the occurrence of health-related events by time, place and person characteristics.

- **Frequency** refers to measurement of frequency of health-related events(disease disability or death) and summarizing this information in the form of rates and ratios.

Descriptive Epidemiology

What ? health-related states or events

Who ? → person

When ? → time

Where ? → place

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Epidemiology: Descriptive Epidemiology

- **Pattern** refers to: **time**, **place** and **person**
- **Time** characteristics:

→ annual occurrence

→ seasonal occurrence

→ daily occurrence (during an epidemic)

→ hourly occurrence (during an epidemic)

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Epidemiology: Descriptive Epidemiology

- **Pattern** refers to: **time**, **place** and **person**
- **Place** characteristics:

→ geographic variation

→ urban-rural differences

→ location of houses, worksites or schools

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Epidemiology: Descriptive Epidemiology

- **Pattern** refers to: **time**, **place** and **person**
- **Personal** characteristics:

→ age
→ race
→ gender
→ marital status
→ Socioeconomic status
→lifestyle behaviors
→occupation
→ environmental exposures

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Epidemiology: Analytic Epidemiology

Determinants

Epidemiologic methods are used as tools to search for causes & other factors that influence the occurrence of health related events → **Analytic Epidemiology**

Why ?

How ?

Relationship between exposure and outcome

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Epidemiologic approaches

DESCRIPTIVE *Health and disease in the community*

What?	Who?	When?	Where?
What are the health problems of the community? What are the attributes of these illnesses?	How many people are affected? What are the attributes of affected persons?	Over what period of time?	Where do the affected people live, work or spend leisure time?

ANALYTIC *Etiology, prognosis and program evaluation*

Why?	How?
What are the causal agents? What factors affect outcome?	By what mechanism do they operate?

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Epidemiology: Epidemiologic Approaches

In very simple terms, the epidemiologist:

- Counts cases or health events, and describes them in terms of time, place, and person;
- Divides the number of cases by an appropriate denominator to calculate rates; and
- Compares these rates over time or for different groups of people.

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Epidemiology: Definition

Health-related states or events include:

- communicable diseases
- non-communicable diseases
- injuries, birth defects
- maternal-child health
- occupational & environmental health
- behaviors related to health (exercise, seat-belt use etc.)

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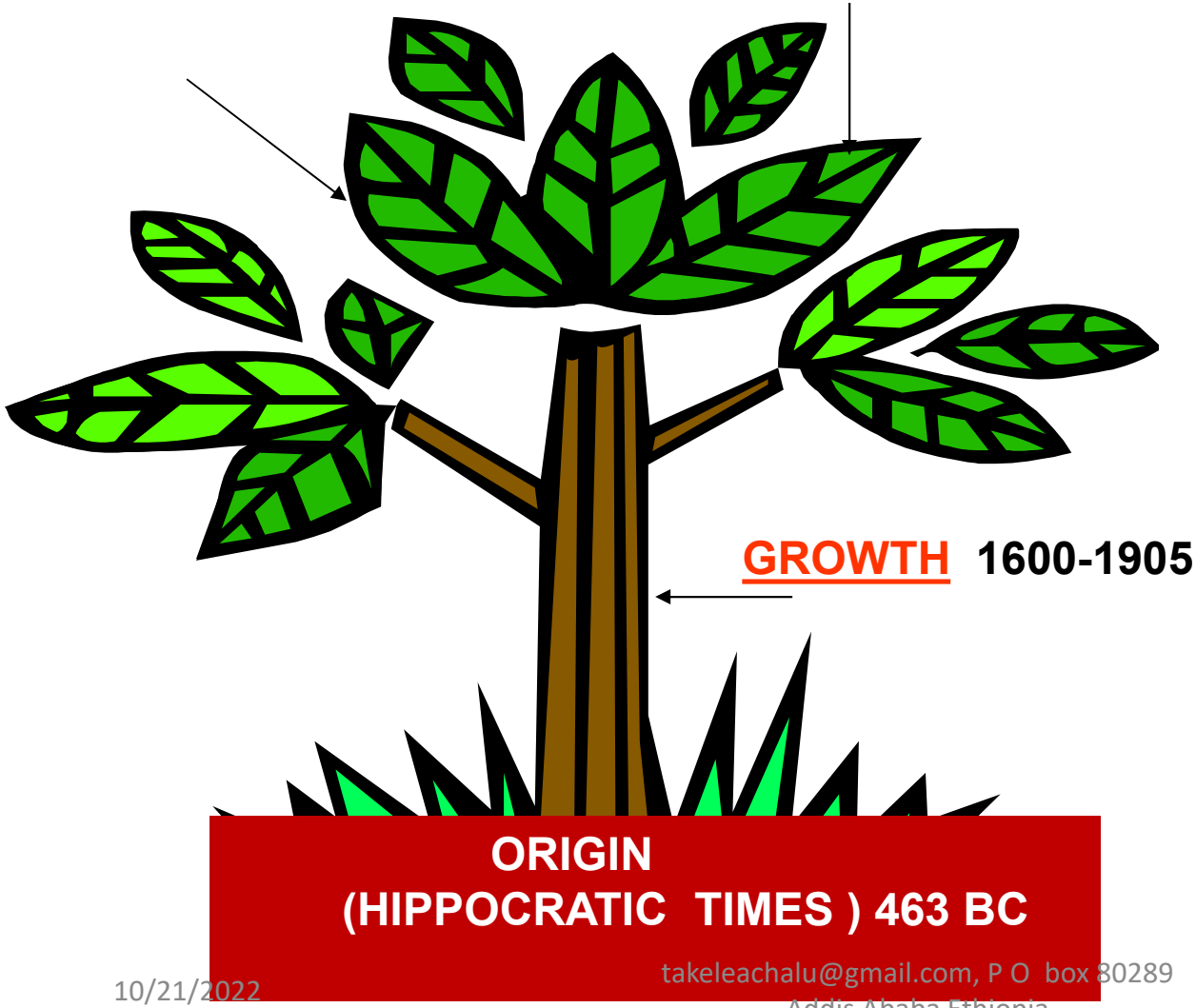
THE ROOTS OF EPIDEMIOLOGY

DEVELOPMENT 1915 – till to date



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Epidemiology: Origin

- HIPPOCRATES planted the seed & the tree of epidemiology has taken its roots in 463 BC

- Described the distribution of diseases by season, age, climate and personal behavior

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Epidemiology: William Farr – Father of Vital Statistics

- Collected & analyzed Britain's morbidity & mortality statistics.

- Examined effects of marital status, occupation, etc on morbidity & mortality statistics

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Epidemiology: John Snow- Father of Modern Epidemiology

- Identified mode of transmission
- Incubation times
- Cause & effect
- Clinical observations of cholera

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Epidemiology: Doll & Hill (1947)

- Studied effect of smoking among a cohort of English doctors
- Well designed epidemiological study
- Demonstrated cause (smoking) and effect (lung cancer)

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Epidemiology: Scopes

- The scope have widened & changed over time
- Started of as a study of epidemics
- Till mid 19th century epidemiology was only a study of epidemics
- Then it became study of infectious diseases,
- later extended to study of non-infectious diseases
- Now has become a discipline that is beyond study of a diseases.

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Epidemiology: Importance

- Clinical Medicine:
  - Its knowledge is important to the clinician in making diagnosis, treatment and prognosis
  - Clinician requires background clinical epidemiological information about a ds i.e incidence rates, sex and age distribution…all these info points to the likely diagnosis while at the same time excluding unlikely diagnosis

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Epidemiology: Importance

Public Health:

- Epidemiology is the cornerstone of Public Health

- It contributed to eradication and control of communicable diseases & to prevention of non communicable diseases

Achievements :

- control of infectious diseases –smallpox and childhood infection by mass immunization,
- effective screening for breast and cervical cancer

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Epidemiology: Importance

Public Health:

- Important in planning and evaluation of health services
- Used to assess the health services
- Data is used for needs assessment
- Evaluation of public health intervention programs
- Evaluation of disease trends by comparing rates over time

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Epidemiology: Function

Epidemiology has major functions:

1. **to describe** patterns of health and disease within populations
2. **to interpret** these differences
3. **to apply** our results to public health practice, and
4. **to evaluate** the effect of health-related interventions

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Epidemiology: Definition

- **Determinants**

Epidemiological methods are used as tools to search for causes & other factors that influence the occurrence of health related

Analytic Epidemiology

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Clinician	Epidemiologist
❖Patient's diagnostician	❖ Community's diagnostician
❖Investigations	❖ Investigations
❖Diagnosis	❖ Predict trend
❖Therapy	
❖Cure	❖ Control
	❖ Prevention

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Cont…

- When faced with a patient with diarrheal disease, for example, the clinician and the epidemiologist have different responsibilities. Although both are interested in establishing the correct diagnosis, the clinician usually focuses on treating and caring for the individual.
- The epidemiologist focuses on the exposure (action or source that caused the illness), the number of other persons who may have been similarly exposed, the potential for further spread in the community, and interventions to prevent additional cases or recurrences.

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Evolution

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Evolution

- Although epidemiologic thinking has been traced from Hippocrates (circa 400 B.C.) through Graunt (1662), Farr, Snow (both mid-1800's), and others, the discipline did not blossom until the end of the Second World War.

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Evolution

Hippocrates (circa 400 B.C.)

- Hippocrates (circa 400 B.C.) attempted to explain disease occurrence from a rational instead of a supernatural viewpoint.
- In his essay entitled “On Airs, Waters, and Places,” Hippocrates
- suggested that environmental and host factors such as behaviors might influence the development of disease

John Graunt (1662)

- quantify patterns of birth, death, and disease occurrence, noting male-female disparities, high infant mortality, urban-rural differences, and seasonal variations.
- No one built upon Graunt’s work until the mid-1800’s

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Evolution

William Farr (mid-1850)

- Began systematically collect and analyze Britain's mortality statistics for the first time .
- considered the father of modern vital statistics and surveillance
- developed many of the basic practices used today in vital statistics and disease classification.
- He extended the epidemiologic analysis of morbidity and mortality data, looking at the effects of marital status, occupation, and altitude.

Evolution

John Snow (1854)

- Was conducting a series of investigations in London
- The father of field epidemiology."
- Snow conducted studies of cholera outbreaks both to discover the cause of disease and to prevent its recurrence.
- His work classically illustrates the sequence from descriptive epidemiology to hypothesis generation to hypothesis testing (analytic epidemiology) to application

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Evolution

- In the mid- and late-1800's, most investigators focused on acute infectious diseases.
- In the 1900's, epidemiologists extended their methods to noninfectious diseases.
- The period since the Second World War has seen an explosion in the development of research methods and the theoretical underpinnings of epidemiology, and in the application of epidemiology to the entire range of health-related outcomes, behaviors, and even knowledge and attitudes.

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Evolution

- The studies by Doll and Hill (13) linking smoking to lung cancer
- the study of cardiovascular disease among residents of Framingham, Massachusetts (12), are two examples of applied epidemiologic methods to chronic disease since World War II.
- Finally, during the 1960's and early 1970's health workers applied epidemiologic methods to eradicate smallpox worldwide. This was an achievement in applied epidemiology

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Why epidemiology ?

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Purposes Of Epidemiology

1. Identify causes and risk factors for disease.
2. Determine the extent of disease in the community.
3. Study natural history and prognosis of disease.
4. Evaluate preventive and therapeutic measures
5. Provide foundation for public policy

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Basic Epidemiologic Assumptions

I. Human disease does not occur at random

- ✓ there are patterns of occurrence in which some behavioral and environmental factors (exposures) increase the risk of acquiring/developing a particular disease among group of individuals.

II. Human disease has causal and preventive factors

- – that can be identified through systematic investigation of populations or group of individuals within a population in different places or at different times.
- – Thus, identifying these factors creates opportunity for prevention and control of diseases in human population either by eliminating the cause or introducing appropriate treatment.

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Models of disease causation

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Model models of disease causation

- Germ theory of disease
- Epidemiological Triad
- Web of Causation theory
- Wheel theory

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Germ Theory of Disease

- Proposed by Robert Koch and Louis Pasteur.
- Every human disease is caused by a microbe or germ, which is specific for that disease and one must be able to isolate the microbe from the diseased human being.

ROBERT KOCH

LOUIS PASTEUR

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Epidemiological Triad

- Through their early study of infectious diseases, epidemiologists began to consider disease states generally in terms of the epidemiologic triad, or the host, agent, and environment model.
- Interactions among these three elements explained infectious and other disease patterns.

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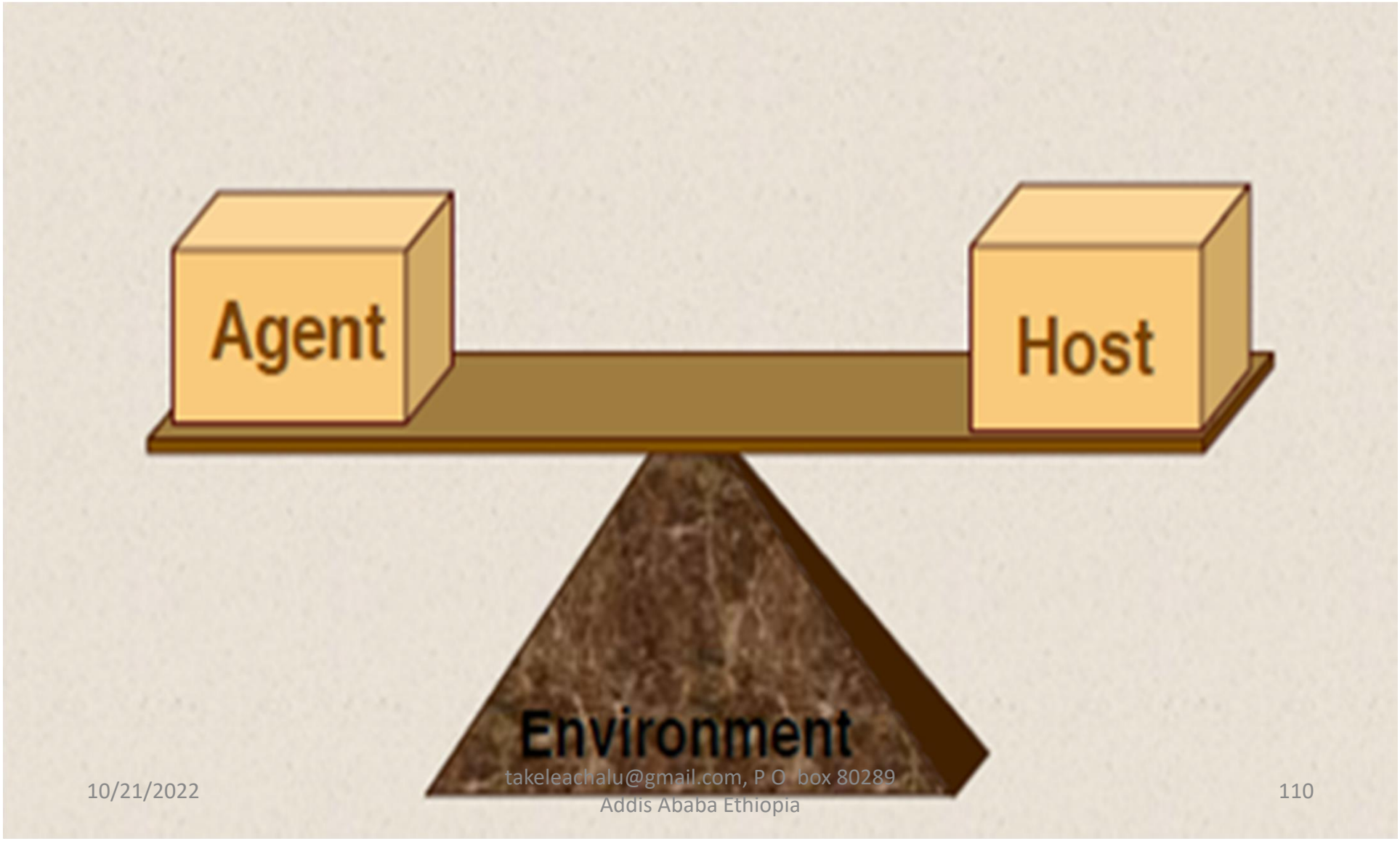
Epidemiological Triad



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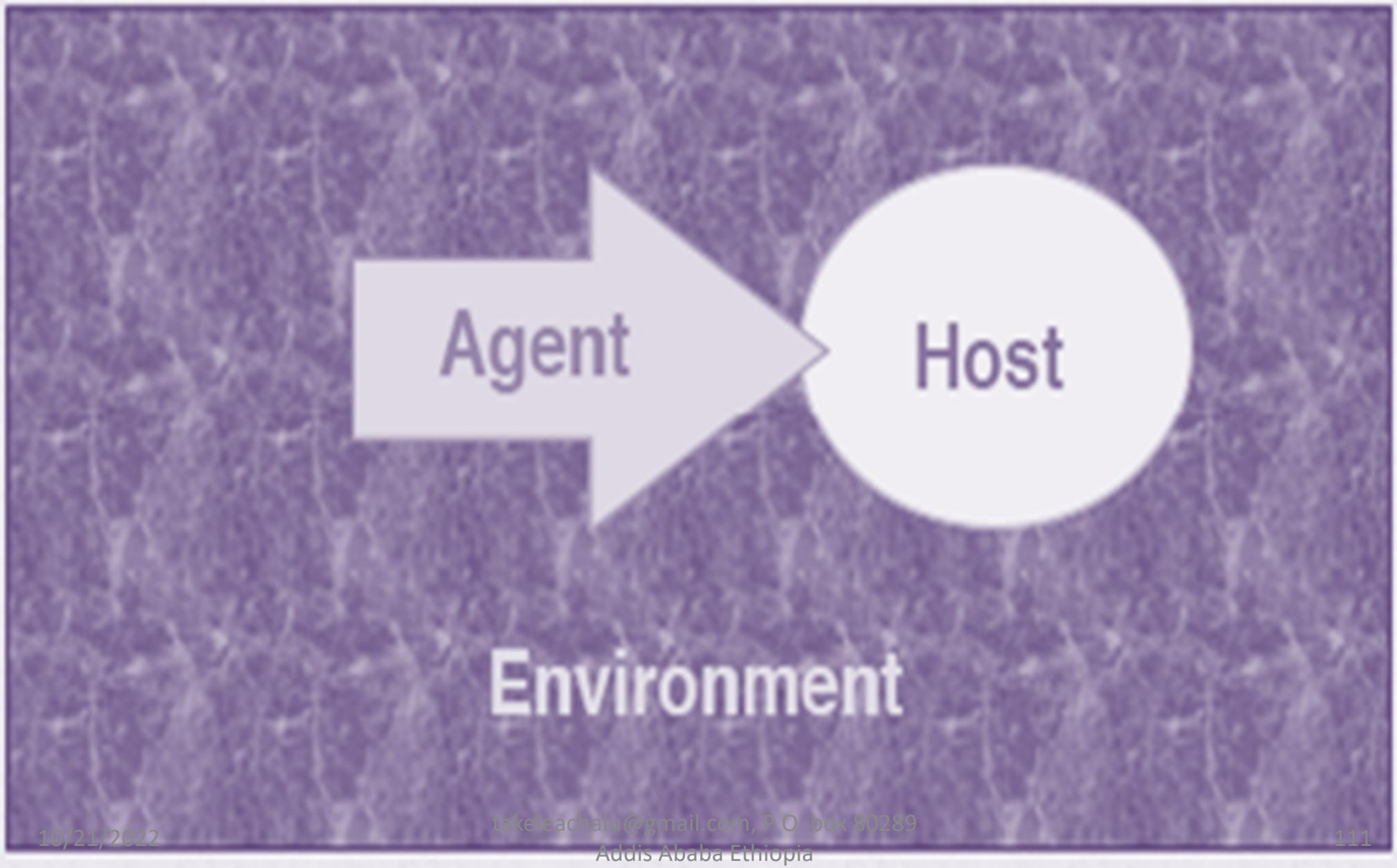
Epidemiological Triad



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Agent

- Is an element or substance, animate or inanimate, the presence (or absence) of which may initiate or perpetuate a disease process.
- A disease may have a single agent, a number of independent alternative agents or complex of two or more factors whose combined presence is essential for the development of the disease.

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Host factors

- are intrinsic factors that influence an individual's exposure, susceptibility, or response to a causative agent.
- Example Age, race, sex, behaviors (smoking, drug abuse, lifestyle, sexual practices and contraception, eating habits) are just some of the many host factors which affect a person's likelihood of exposure.
- Age, genetic composition, nutritional and immunologic status, anatomic structure, presence of disease or medications, and psychological makeup are some of the host factors which affect a person's susceptibility and response to an agent.

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Environment

- The environment refers to all the external factors surrounding the host that might influence vulnerability or resistance.
- Environmental factors are extrinsic factors which affect the agent and the opportunity for exposure.
- Generally, environmental factors include physical factors such as geology, climate, and physical surroundings (e.g., a nursing home, hospital); biologic factors such as insects that transmit the agent; and socioeconomic factors such as crowding, sanitation, and the availability of health services.

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CAUSE

- **Cause is an antecedent event, condition or characteristic that was necessary for the occurrence of the disease at the moment it occurred, given other conditions are fixed.**

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A. WHY DO WE NEED TO UNDERSTAND CAUSE?

- **It helps in preventing disease, diagnosis and appropriate treatment**

- Causal complements of factors are the necessary and sufficient condition for a factor to produce disease

- To understand causation, knowledge of concepts like: necessary, sufficient, biologic (etiologic) cause, strengths of effects and interaction are necessary

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CONCEPTS OF SUFFICIENT CAUSE AND NECESSARY CAUSES

- **Sufficient cause (a complete causal mechanism)=> is a set of minimal conditions and events that inevitably produce disease**
- **Necessary- disease can not develop in its absence**
- **In disease etiology (etiologic cause) may be considered completion of a sufficient cause equivalent to onset of disease process rather than onset of clinical signs and symptoms**

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Concept of Cause

- Cause of a disease is an event, a condition, characteristics or a combination of these factors which plays a role of producing a particular disease.
  - **Sufficient** Vs **necessary** causes
  - A sufficient cause is not usually a single factor.
  - A necessary cause, is a factor that is necessary (or with out which) the disease doesn't exist or occur

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The four types of causal relations

1. **Necessary and sufficient:** a factor is both necessary (i.e., disease will occur only if the factor is present), and sufficient (i.e., exposure always leads to disease).
   - This type of relationship is rarely encountered.

2. **Necessary but not sufficient:** more than one factor is required, usually in a temporal sequence.
   - TB
   - The initiation and promotion stages associated with carcinogenesis models

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3. **Sufficient but not necessary:** a specific factor can cause a disease process, but other factors by themselves can cause the same disease.
   - Vitamin B_{12} deficiency can cause an anemia, but other factors can result in anemia as well.

4. **Neither sufficient nor necessary:** a specific factor can be combined with other factors to produce a disease. However, the disease may be produced even in the absence of the factor.
   - Usually in chronic diseases; multiple risk factors for the development of atherosclerotic heart disease are neither sufficient nor necessary

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Concept of Cause

- Each sufficient cause has a necessary cause as a component (especially for infectious disease).

- It is not necessary to identify all components of sufficient cause, because one component can interfere with the action of the others.

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Natural history of disease

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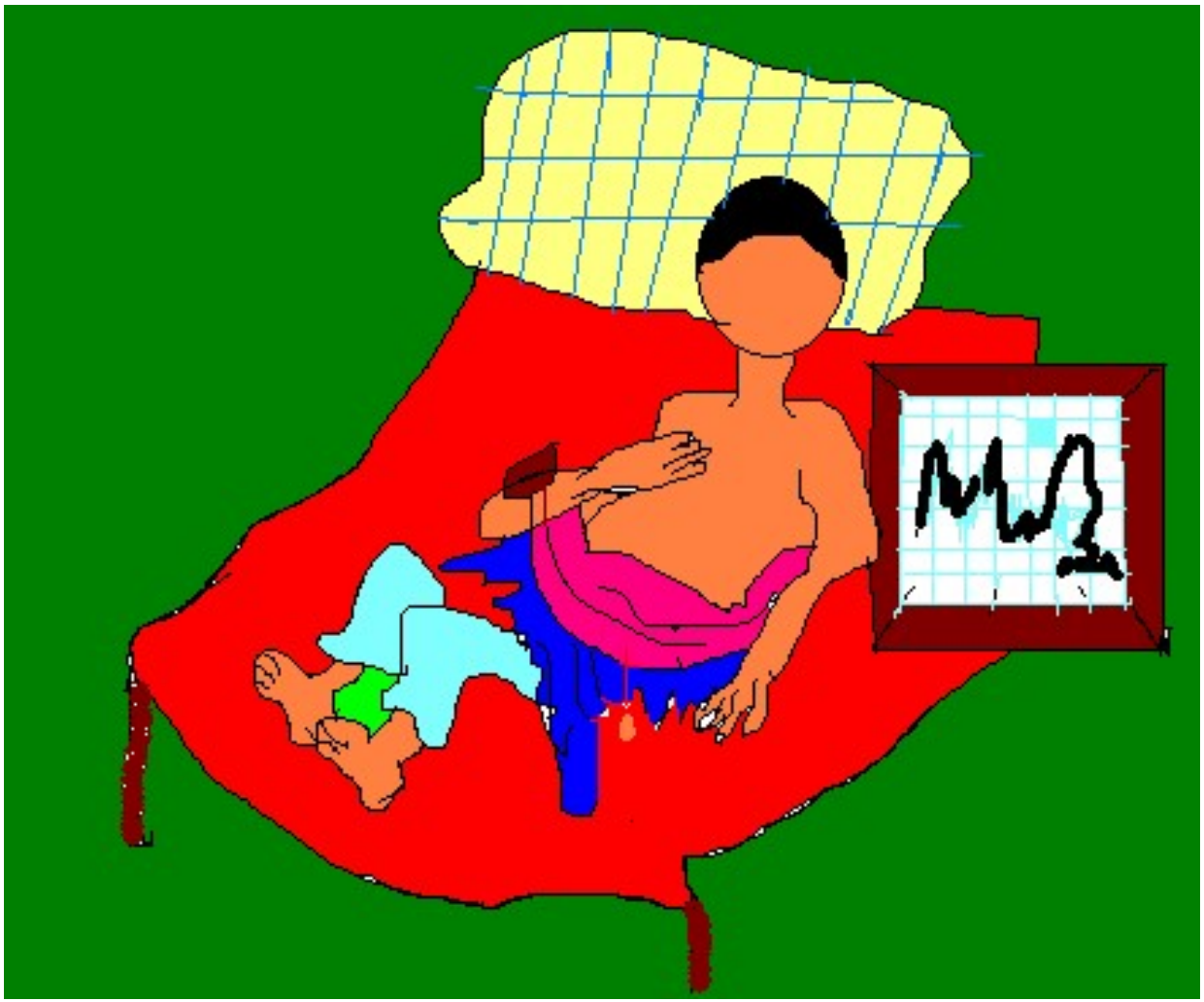
Health and disease



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Disease

- What is Disease?

The biological process that doctors use to explain and understand illness

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Illness

- What is Illness?

Definitions vary and patients and doctors will disagree!

The patients experience of a physical or psychological disturbance

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The soundness of body and mind is called Health.

A healthy person is one who is physically and mentally fit in all respects.

Good health makes a man happy and cheerful but some-times a healthy person can also fall ill.

Person may get diseases like Viral fever, Malaria etc.

The illness(or sickness) is called disease.

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Characteristics of good health.

- *The person has capability to do work.*
- *The person feels himself efficient to take decisions and work accordingly .*
- *The person remains in sound mental condition.*
- *The person remain free from any disease.*
- *The person does not suffer from mental tension.*

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Requirements of good health

We all know that , Good health essential for Leading purposeful life.

For maintaning a good health following conditions are ***essential.***

1. ***Nutrition***
2. ***Exercise and rest***
3. ***Good habits***

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The World Health Organisation definition:
Health is a state of complete **physical**, **mental** and **social well-being** and not merely the absence of disease or infirmity.

Disease can be:

- **Communicable** – these are **infectious** diseases caused by viruses, bacteria, protists and fungi and are **spread** in animals (and plants) e.g. malaria, measles, athletes foot
- **Non-communicable** – these diseases are not caused by **infection** and cannot be **spread** e.g. heart disease, diabetes, Alzheimer's, asthma

Different **types of disease** may **interact** (work together) to make a person more **susceptible** to other diseases.

- **Defects in the immune system** mean that an individual is more likely to suffer from infectious diseases
- **Viruses** living in cells can be the trigger for cancers to form
- **Immune reactions** initially caused by a pathogen can trigger allergies such as skin rashes and asthma
- **Severe physical ill health** can lead to depression and other mental illness

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Definition

- ✓ **Natural history of disease** refers to the progress of a disease process in an individual over time, in the absence of intervention.
- ✓ The process begins with exposure to or accumulation of factors capable of causing disease.
- ✓ Without medical intervention, the process ends with
  - ✓ recovery ,
  - ✓ disability,
  - ✓ or death.

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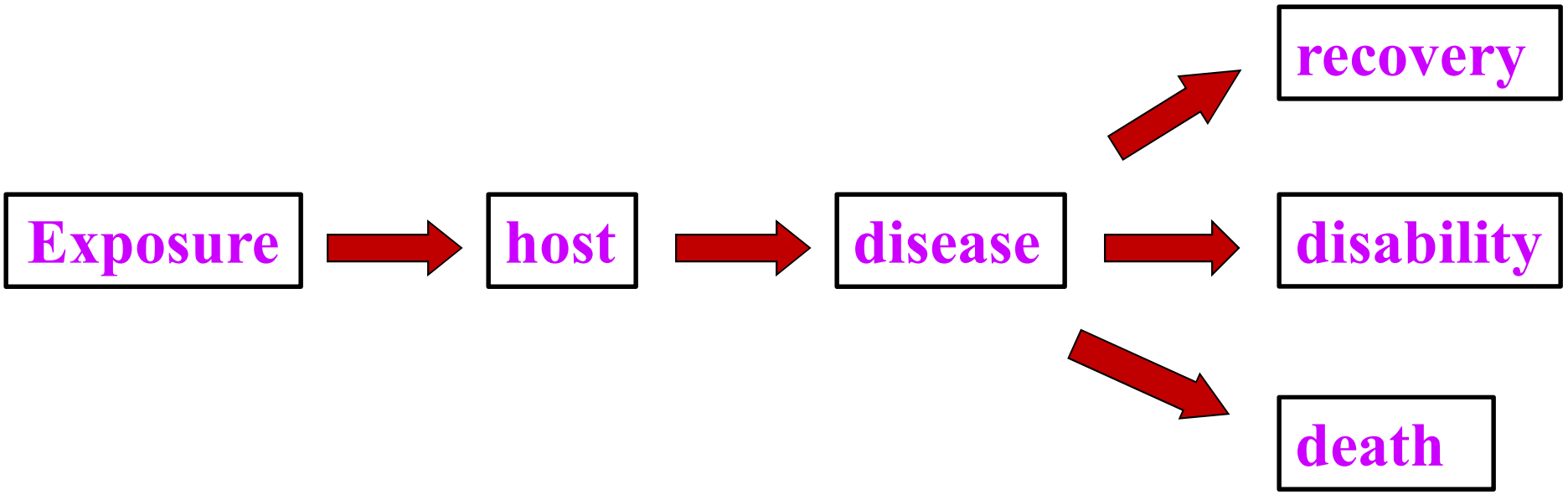
Natural History of Disease



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Natural History of diseases

- **The natural history of a disease refers to the progress of a disease process in an individual over time, in the absence of intervention.**
- **It begins with an exposure of a susceptible host to a causative agent.**
- **With out medical intervention, the process ends with *recovery, disability* or *death*.**
- **Usual course of a disease may be halted at any point in the progression by preventive and therapeutic measures.**

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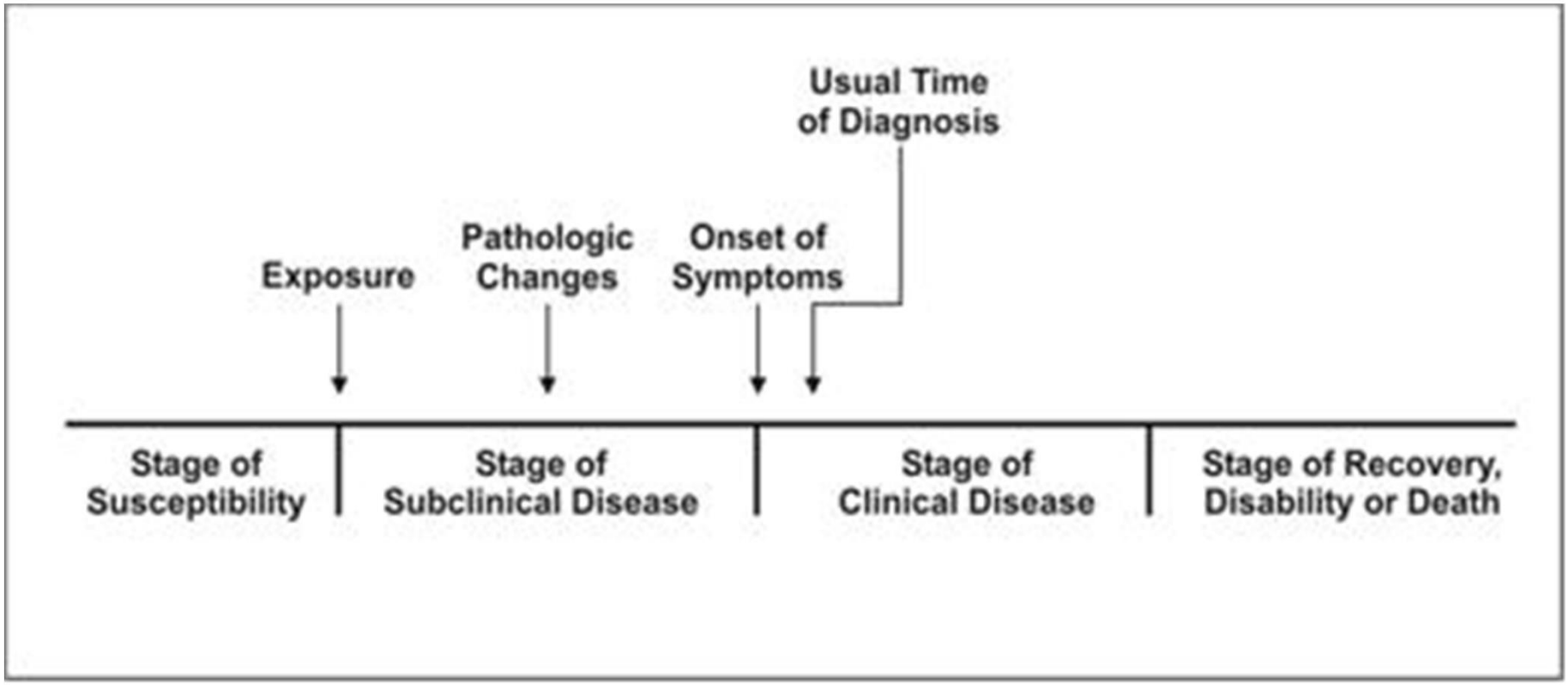
Natural history /spectrum /timeline of disease



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Natural history of disease

- Detection and treatment at any stage can alter the natural history of a disease, but the effects of treatment can only be determined if the natural history of the disease in the absence of treatment is known.

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Cont…

- ✓ Usually, a period of subclinical or in apparent pathologic changes follows exposure, ending with the onset of symptoms.
- ✓ For infectious diseases, this period is usually called **the incubation period**
- ✓ for chronic diseases, this period is usually called **the latency period.**
- ✓ This period may be **as brief as seconds** for hypersensitivity and toxic reactions to **as long as decades** for certain chronic diseases.

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Cont…

- The onset of symptoms marks the transition from subclinical to clinical disease.
- Most diagnoses are made during the stage of clinical disease.
- In some people, however, the disease process may never progress to clinically apparent illness.
- In others, the disease process may result in a wide spectrum of clinical illness, ranging from mild to severe or fatal.

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Cont…

- Three terms are used to describe an infectious disease
- **Infectivity** refers to the proportion of exposed persons who become infected.
- **Pathogenicity** refers to the proportion of infected persons who develop clinical disease.
- **Virulence** refers to the proportion of persons with clinical disease who become severely ill or die.

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Disease prevention

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Disease prevention

- Disease prevention means avoiding disease occurrence, interrupting or slowing the progression of disease, minimizing the prognosis of disease .
- Therefore, the aim is to push back the level of detection and intervention to the precursors and risk factors of disease.
- Fluctuation in patterns of morbidity and mortality over time in countries indicate that causes of disease are preventable.
- Hence, epidemiology plays a central role in disease prevention by identifying those modifiable causes.

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Primordial prevention

- Prevention of the emergence or development of risk factors.
- Particularly useful for chronic diseases.
- Example :Many adult health problems (e.g., obesity, hypertension) have their early origins in childhood, because this is the time when lifestyles are formed (smoking, eating patterns, physical exercise).
- Efforts are directed towards discouraging children from adopting harmful lifestyles.
- The main intervention – is through individual and mass education.

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Primary prevention

- Its aim is to protect an individual from having the disease of interest
- Measures of prevention undertaken during the phase of pre-pathogenesis (phase of susceptibility)
- Involves two sub-steps: **Non specific protection** and specific protection

Non specific protection: Steps undertaken to improve the level of general health and well being so that conditions for initiation of disease process are prevented.

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Primary prevention

- **Non specific protection includes**
  - improvement in the overall socio-economic status of the population,
  - health education,
  - feeding programmes for mothers and children,
  - promotion of breast feeding
  - promotion of small family norms
  - education
  - motivation for healthy lifestyle.

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Primary prevention

- **Specific Protection** : include measures to prevent the initiation of specific diseases or a group of diseases.
- Examples
  - Immunization to protect against specific diseases
  - Fortification of foods with specific nutrients (as salt with iodine)
  - Use of condoms to protect against sexually transmitted diseases (STDs)
  - Use of helmets to protect against head injuries

Level of prevention

There are several stages during the course of a disease at which we can intervene in order to control the disease.

Three levels, (Primary, secondary and tertiary)

A. Primary prevention

The objectives here are to *promote health*, *prevent exposure,* and *prevent disease.*

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Cont…

1. **Health promotion:**

- **This consists of general non-specific interventions that enhance health and the body's ability to resist disease – including:**

- **The improvement of socioeconomic status through the provision of adequately.**
  - **paid jobs,**
  - **education,**
  - **affordable and adequate housing and clothing, etc.**

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Cont…

2. Prevention of exposure:

- **There are many examples of interventions aimed at this stage, such as**
  - **the provision of safe and adequate water, of proper excreta disposal,**
  - **Provision of vector control;**

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Cont…

- **Provision of a safe environment at home**

- **Example;**
  - **proper storage of insecticides and medicines, out of children's reach),**

  - **on the streets (e.g., driver licensing laws).**

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Cont…

3. Prevention of disease:

- **An example of intervention, which acts at this stage, is immunization.**
- **Breastfeeding is an example of an intervention which acts at all three levels of primary prevention.**

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Cont…

B. Secondary prevention

- **After the biological onset of disease, but before permanent damage sets in , we speak of secondary prevention.**

- **The objective here is to stop or slow the progression of disease so as to prevent or limit permanent damage.**

- **Strategy at this stage is through *early detection* and *treatment* of disease.**

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Secondary Prevention

- These include all actions undertaken at the stage of early pathogenesis (asymptomatic disease) with a view **to halt the progress of disease at it's earliest, incipient stage, by "early diagnosis and prompt treatment".**
  - classical example is "**screening for disease**" for breast cancer (using mammography) and cervical cancer (using pap smear).
  - **medical examinations of school children, of industrial workers and various disease screening camps.**

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Cont…

c. Tertiary prevention

- **After permanent damage has set in, the objective of tertiary prevention is to limit the impact of that damage.**

- **The impact can be physical, psychological, social (social stigma or avoidance by others), and financial.**

- **Strategy at this stage in general is *rehabilitative.***

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Tertiary prevention

- These include all measures undertaken when the disease has become clinically manifest or advanced, with a view **to prevent or delay death, reduce or limit the impairments and disabilities, minimize suffering and to promote the subject's adjustment to irremediable conditions.**

- Tertiary prevention has two types of approaches
  - **disability limitation**
  - **rehabilitation**.

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Tertiary prevention

- **Disability Limitation** : These include all measures to prevent the occurrence of further complications, impairments, disabilities and handicaps or even death. example :
  - Application of plaster cast to a patient who has suffered Colle's fracture, is done to prevent complications and further disability like mal-union or non-union.
  - Complete rest, morphine, oxygen and streptokinase is given to a patient of Acute MI, to prevent death or complications like arrhythmias / CHF.

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Tertiary prevention

- The sequence with which a disease turns into a handicap is as follows :
  - **Impairment :** This is the actual loss or damage of a part of body anatomy or an aberration of the physiological functions that occurs consequent to a disease.
  - **Disability :** This is defined as the inability to carry out certain functions or activities which are otherwise expected for that age / sex, as a result of the impairment.
  - **Handicap :** This is the final disadvantage in life which occurs consequent to an impairment or disability, which limits the fulfillment of the role a person is required to play in life.

Tertiary prevention

- **Rehabilitation** : This is the second component of tertiary prevention.
- Rehabilitation stands for the combined and coordinated usage of all the available medical, social, educational and vocational measures, for training the person to the highest level of functional ability.

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Tertiary prevention

- **Medical rehabilitation**
  - This is done through medical / surgical procedures to restore the anatomy, anatomical functions and physiological functions to as near normal as possible.
- **Vocational rehabilitation**
  - It includes steps involving training and education so as to enable the person to earn a livelihood.

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Cont…

- **Social rehabilitation**
  - This involves steps for restoration of the family and social relationships.
- **Emotional and Psychological rehabilitation :**
  - This involves steps to restore the confidence, personal dignity and confidence.

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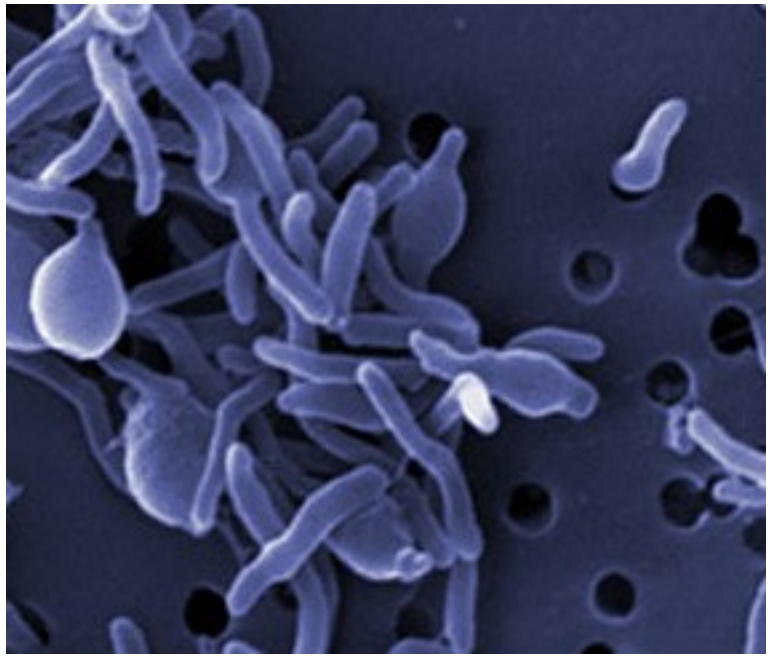
Infectious Diseases are defined as:

"Disorders caused by organisms, such as bacteria, viruses, fungi or parasites …which can be passed from person to person. Some are transmitted by insect or animal bites while others are passed by ingesting contaminated food or water or being exposed to organisms in the environment."



Infectious disease cycle

- A communicable (or infectious) disease is one caused by transmission of a specific pathogenic agent to a susceptible host.

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Chain of infection

- Communicable diseases occur as a result of the interaction between:
  - the infectious agent
  - the transmission process(reservoir, portal of exit, portal of entry)
  - susceptible host
  - the environment.
- The control of such diseases may involve changing one or more of these components, all of which are influenced by the environment.
- These diseases can have a wide range of effects, varying from silent infection – with no signs or symptoms – to severe illness and death.

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Cont…

- Three terms are used to describe an infectious disease
- **Infectivity** refers to the proportion of exposed persons who become infected.
- **Pathogenicity** refers to the proportion of infected persons who develop clinical disease.
- **Virulence** refers to the proportion of persons with clinical disease who become severely ill or die.

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component of chain of infection

1. **Causative Agent**
2. Reservoir host
3. Portal of exit
4. Mode of transmission
5. Portal of entry
6. Susceptible **host.**

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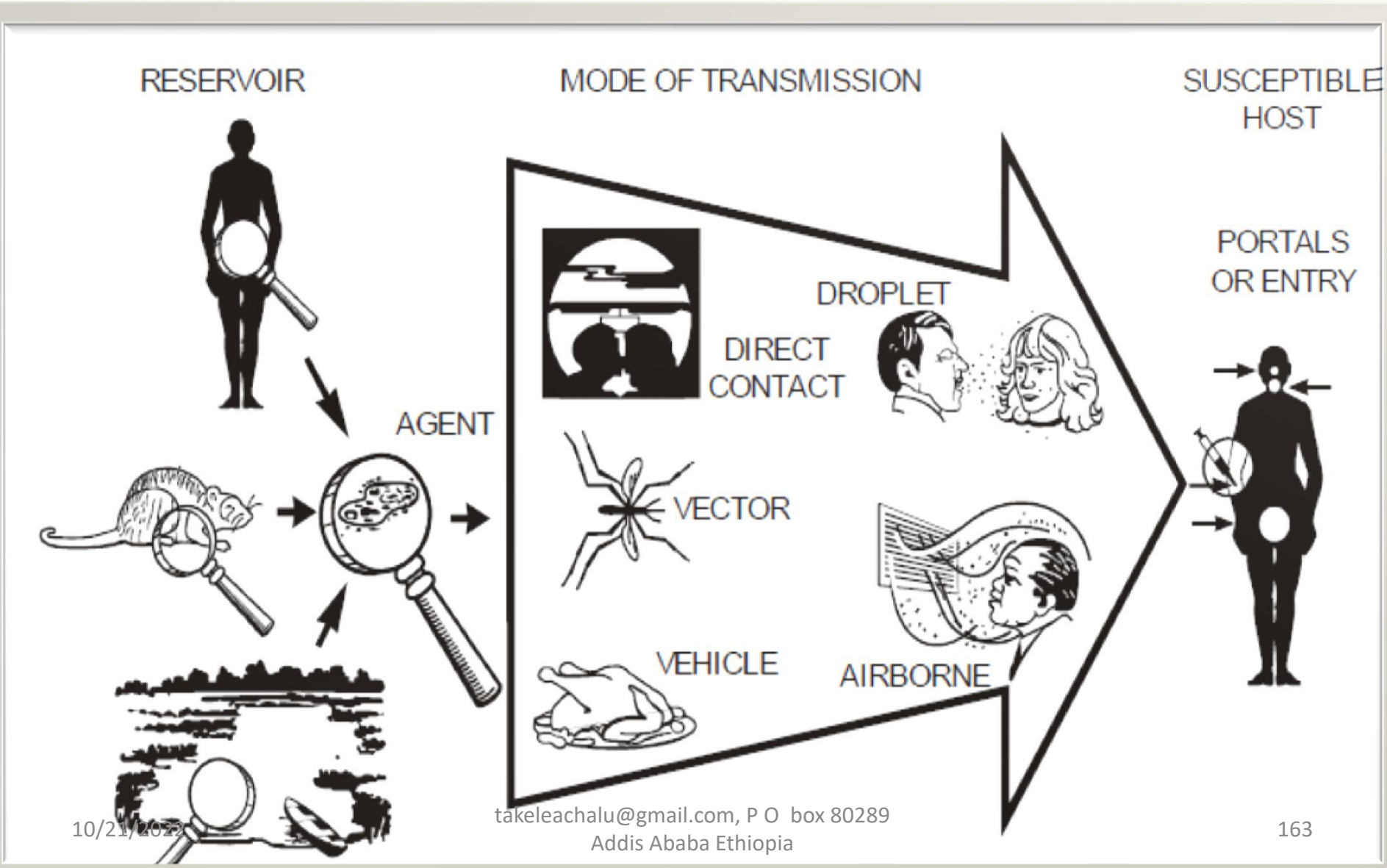
Infectious disease cycle



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Reservoir

- ✓ The habitat in which an infectious agent normally lives, grows, and multiplies.
- ✓ Include
  - ❑ **Human**
  - ❑ **Animal**
  - ❑ **Environment**

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Human reservoirs

- Many of the common infectious diseases have human reservoirs.
- Diseases which are transmitted from person to person without intermediaries have human reservoirs. e.g. measles ,STI
- Smallpox was eradicated after the last human case was identified and isolated because humans were the only reservoir for the smallpox virus.
- Two types of human reservoir exist:
  - **persons with symptomatic illness**
  - **carriers**

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carrier

- A carrier is a person without apparent disease who is capable of transmitting the agent to others.

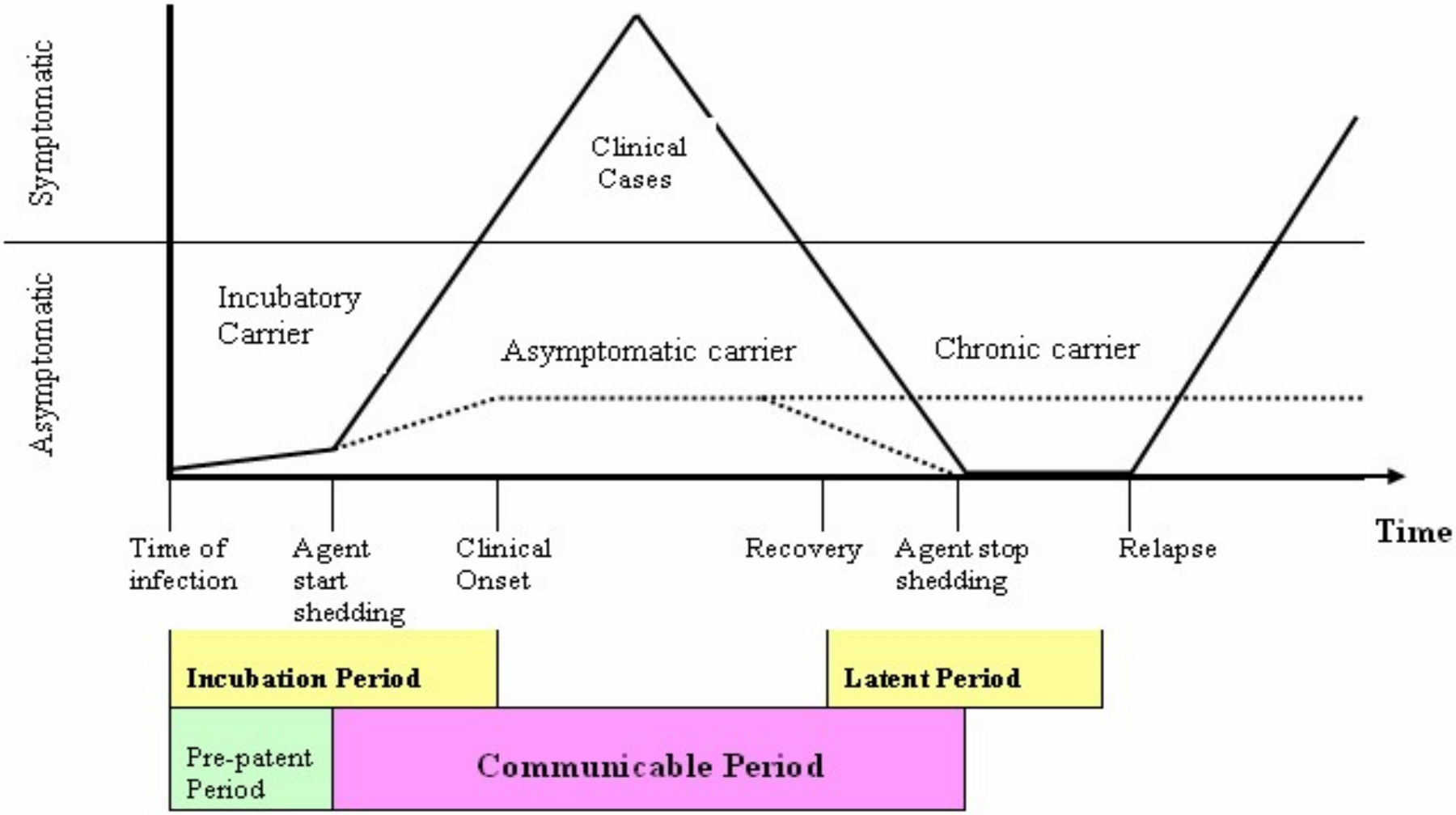
  I. **asymptomatic carriers, who never show symptoms during the** time they are infected,

  II. **incubatory or convalescent carriers, who are capable of** transmission before or after they are clinically ill.

  III. A **chronic carrier is one who continues to** harbor an agent

- Symptomatic persons are usually less likely to transmit infection widely because their symptoms increase their likelihood of being diagnosed and treated, thereby reducing their opportunity for contact with others.

Time Course of a Disease in Relation to Its Clinical Expression and Communicability



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Animal reservoirs

- **Zoonotic disease**
  - brucellosis (cows and pigs),
  - anthrax (sheep),
  - plague (rodents),
  - trichinosis (swine),
- **And other**

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Environmental reservoirs

- ✓ **Plants, soil, and water in the environment are also reservoirs for** some infectious agents. Many fungal agents, such as those causing histoplasmosis, live and multiply in the soil.
- ✓ The primary reservoir of Legionnaires' bacillus appears to be pools of water, including those produced by cooling towers and evaporative condensers.

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Portal of exit

- The path by which an agent leaves the source host.
- Usually corresponds to the site at which the agent is localized.
- Here below are some of the microorganism with their portal of exit

  - **Tubercle bacilli ----respiratory tract**
  - **schistosomes ----urine**
  - ***Sarcoptes scabiei ----skin lesion***
  - **Hepatitis B----- body fluid**

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. Modes of transmission

1. Direct transmission –

- **direct transfer of etiologic agent from host or reservoir to susceptible person.**

***A. Direct contact spread* - kissing, sexual transmission, faeces-hand-mouth in shigellosis, skin-to-skin, biting (rabies), etc.**

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Modes of Transmission

- ✓ After an agent exits its natural reservoir, it may be transmitted to a susceptible host in numerous ways.
- ✓ These modes of transmission are classified as

II: **Direct**

- — Direct contact
- — Droplet spread

II: Indirect

- – Airborne
- – Vehicle borne
- – Vector borne
  1. **Mechanical**
  2. **Biologic**

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Direct transmission

- Immediate **transfer of the agent** from a reservoir to a susceptible host **by direct contact or droplet spread.**
- Example of direct contact
  - Kissing
  - skin-to-skin contact
  - sexual intercourse
  - contact with soil or vegetation
  - Droplet spread
- **Droplet spread** refers to **spray with relatively large, short-range aerosols** produced by **sneezing, coughing, or even talking.**
- Droplet spread is classified as direct because transmission is by direct spray over a few feet, before the droplets fall to the ground.

Mode of Indirect transmission

❑ Vector

I. Mechanical transmission

❖ the agent does not multiply or undergo physiologic changes in the vector

- Flies carry Shigella on appendages
- Fleas carry Yersinia pestis.

II. Biologic transmission.

– an agent undergoes part of its life cycle inside a vector before being transmitted to a new host.

– When the agent undergoes changes within the vector, the vector is serving as both an intermediate host and a mode of transmission.

» **Anopheles mosquito - malaria**

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Mode of Indirect transmission

❑ Vehicle

- May passively carry an agent
- may provide an environment in which the agent grows, multiplies, or produces toxin
- it can be:-
  - **Food**
  - **Water**
  - **Biologic products (blood)**
  - **Fomites**

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Mode of Indirect transmission

Airborne transmission

- Transmission by particles that are suspended in air.
- There are two types of particles:

I: Dust

- infectious **particles blown from the soil by the wind**
- **material** that has **settled on surfaces and become re-suspended by air currents.**

II: Droplet nuclei

- **are the residue of dried droplets.**
- **less than 5 µ (microns)** in size
- may remain suspended in the air for long periods
- are easily inhaled into the lungs and exhaled.
- **Tuberculosis**

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Cont…

- It is important to distinguish between types of transmission when selecting control methods.
- Direct transmission can be interrupted by preventing contact with the source; indirect transmission requires different approaches, such as the provision of mosquito nets, adequate ventilation, cold storage for foods or sterile syringes and needles

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Portal of entry

- **A path in which an agent enters to the susceptible host**
- Provide access to tissues in which the agent can multiply or a toxin can act.
- It may be the same with portal of entry (**influenza virus – its exit and entry is the respiratory tract)**
- **It can be :-**
  - **Mouth**
  - **skin (hookworm)**
  - **mucous membranes (syphilis, trachoma)**
  - **blood (hepatitis B).**
  - **Fecaloral if the exit of an agent is feces and its entry through mouth**

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Host

- **The final link** in the chain of infection is a **susceptible host**
- Susceptibility of a host depends on:-
  - **Genetic factors**
  - **Specified acquired immunity (active and passive immunity)**
  - **General factors(skin, mucousmabrane,cilia …etc)**
    - **malnutrition ,**
    - **Alcoholism**
    - **Therapy**

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Disease classification

- Disease is often classified according to:
- 1) its time course, or
- 2) its cause.
- The time course classifies disease as
  - acute (characterized by a rapid onset and short duration) or
  - chronic (characterized by a prolonged duration). A chronic disease may have both acute and chronic manifestations.

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Basic epidemiologic measurement

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Types of Epidemiologic Measures

1. **Measures of disease frequency**

2. **Measures of association**

3. **Measures of potential impact**

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Measures of disease frequency

- Count
- Ratio
- Proportion
- Rate

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Count

- **Simplest & most basic measure**
- **Absolute number of persons who have disease or characteristic of interest.**
- **Useful for health planners & administrators**: for allocation of resources (e.g. quantity of ORS needed by diarrheal cases)
- **Also used for surveillance** of infectious disease for early detection of outbreaks.

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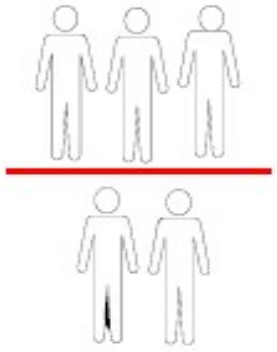
Ratio

- ✓ Ratio is the **relative size of two quantities**
- ✓ It quantifies the magnitude of occurrence of something in relation to another.
- ✓ One number divided by another number
- ✓ The **magnitude of one character divided by another**

  Example: sex ratio



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Ratio Example

What is the ratio of females to males?

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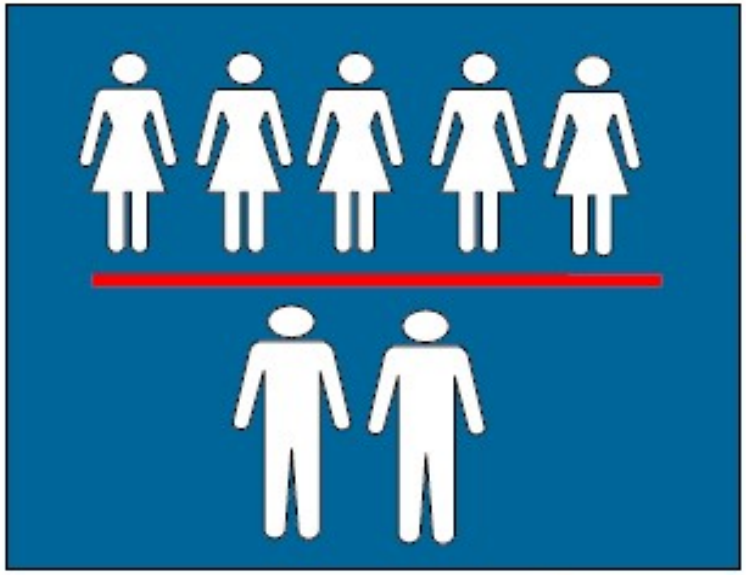
Ratio Example

What is the ratio of females to males?

$$\frac{\#\ \text{Females}}{\#\ \text{Males}}$$



= 5 / 2 = 2.5:1 = 2.5

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Ratio — Different Variables

A city of 4 million people has 400 clinics.
Calculate the ratio of clinics per person.

Ratio = 400 / 4,000,000 = 0.0001 clinics / person

Multiply by 10^4

Ratio = 0.0001×10^4 = 1 clinic / 10,000 persons

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Ratio — Comments

- Common descriptive measure
- Numerator and denominator can be unrelated
- Either numerator or denominator usually set to 1

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Proportion

- ✓ It is a ratio of two quantity in which Numerator included in the denominator
- ✓ Its result ranges between 0 and 1 or (0–100%)
- ✓ Parcentage = Proportion x 100

- **Proportion:** + a included in the denominator

$$\frac{a}{a+b}$$

+ No measurement unit; > 0 to ≤ 1

+ Often expressed as %

Example: From 7,999 females aged 16 – 45 y, 2,496 use modern contraceptive methods.

The proportion of those who use modern contraceptive methods = 2,496 / 7,999 x 100 = 31.2%

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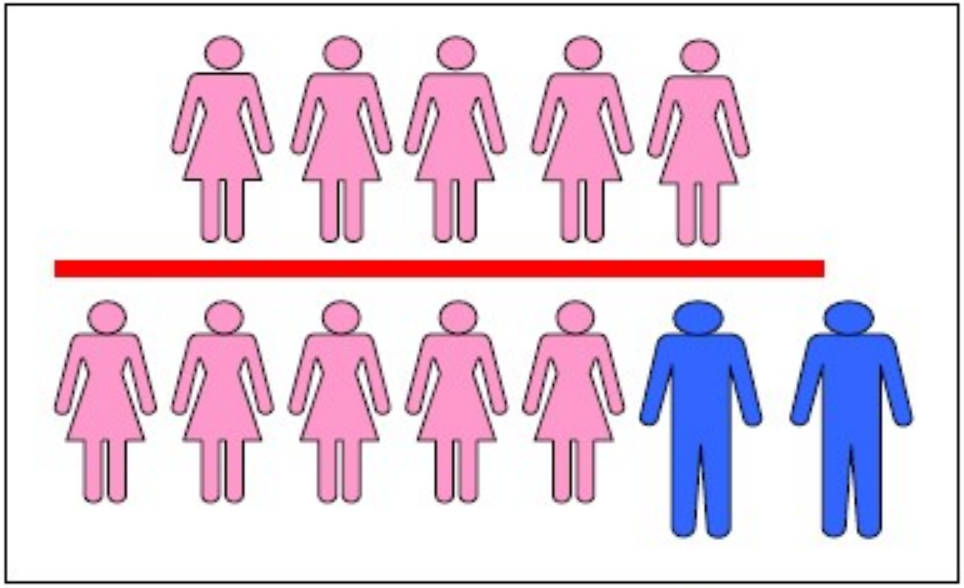
Proportion Example

What proportion of the group is female?

$$\frac{\#\ \text{Females}}{\text{Total}}$$



= 5 / 7 = 0.714

= 71.4%

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Proportion — Comments

- Common descriptive measure
- Numerator must be included in the denominator
- Can be expressed as a fraction, decimal, or percentage

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4. Rate

- **Rate**: measures the occurrence of an event in a population over time.

  - It is similar to proportion
  - But it also adds **time dimension**

$$\frac{\text{Cervical cancer cases in menopausal women in 2000}}{\text{Total number of menopausal women in 2000}}$$

Rates must:-

I. Include persons in the denominator who reflect the population from which the cases in the numerator arose

II. include counts in the numerator which are for the same time period as those from the denominator

III. include only persons in the denominator who are "at risk" for the event.

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Summary

- All rates are proportions!
- All rates are ratios too!
- All proportions are ratios!
- But all proportions are not rates!
- All ratios are not proportions!

Fundamentally important measures of morbidity

1. Prevalence

Which measures a population's disease status (two forms)

1. Point Prevalence
2. Period prevalence

2. Incidence

Assesses frequency of disease onset (two forms)

1. Cumulative incidence/ incidence proportion
2. Incidence density or incidence rate

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Incidence

- Number of new cases of a disease which come into being during a specified period of time.

  (Number of new cases of specific disease during a given period)/(population at risk during that period) x 1000

  Importance: If incidence increasing, it may indicate failure or ineffectiveness of control measure of a disease and need for better/new health control measure.

Relationship between incidence and prevalence

- Prevalence =Incidence x Duration

Incidence

- Is number of new case of disease that occur during a specified period of time in a population at risk for developing the disease
- Two types
  - Cumulative incidence
  - Incidence rate(Density)

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Incidence rate

= new cases occurring during a given time period × 10n

population at risk during the same time period

- ✓ **It is a measure of the frequency** with which an event occurs in a population over a period of time.
- ✓ **It** indicates *how quickly people become ill measured in people per year (the speed of disease occurrence)*
- ✓ The numerator of an incidence should reflect **new cases of disease which occurred or were diagnosed during the specified period.**
- ✓ **The numerator should not include cases** which occurred or were diagnosed earlier.
- ✓ **Persons who are included in the denominator should be able to the disease** that is being described during the time period covered.
- ✓ **Denominator is can be average size of the population over the time period, size of the population at the middle of the time period/person time at risk /population at risk**
- ✓ **Its synonyms are incidence, incidence density/person time rate**

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Example -I

- In 1989, 733,151 new cases of gonorrhea were reported among the Ethiopian population. The 1989 mid-year Ethiopian population was estimated to be 246,552,000. calculate the 1989 gonorrhea incidence rate.

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Solution

Given

- no of new case= *733,151*
- Estimated middle year population =*246,552,000*
- 10n = 100,000

Required ? incidence rate

Solution

Incidence rate = (*733,151/ 246,552,000)x(105)= 297.4 per 100,000per year or

or

Approximately 3 reported cases per 1,000 population in 1989.

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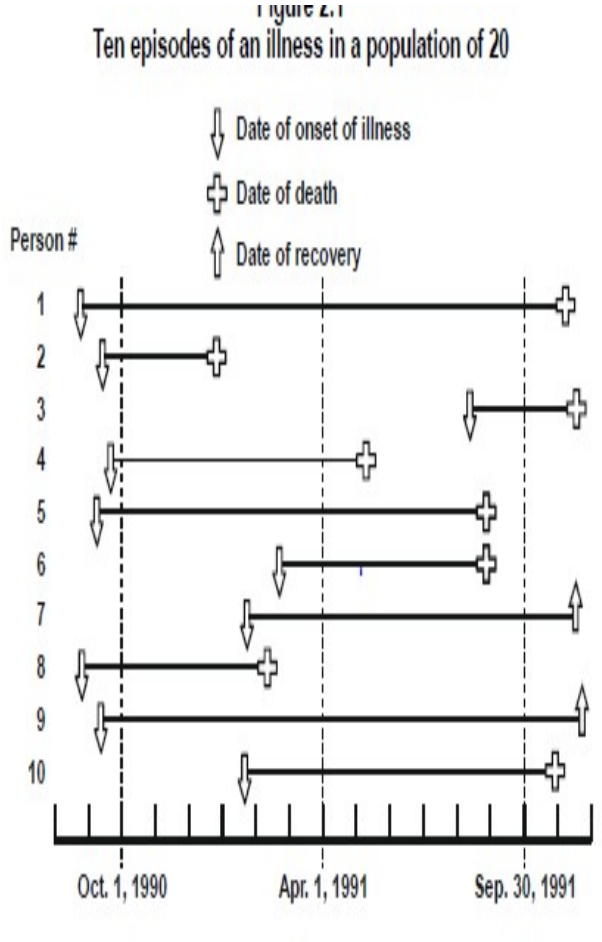
Example2

- Figure 2.1 represents ten episodes of an illness in a population of 20 over a period of 16months. Each horizontal line represents the portion of time one person spends being ill. The line begins on the date of onset and ends on the date of death or on the date of recovery.
- In this example we will calculate the incidence rate from October 1, 1990 to September 30, 1991, using the midpoint population as the denominator.



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Solution

x = new cases occurring 10/1/90–9/30/91 = 4

y = total population at midpoint = 20 – 2 = 18

$$\frac{x}{y} \times 10^n = \frac{4}{18} \times 100 = \frac{22}{100}$$

So the one-year incidence was 22 cases per 100 population.

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Cumulative Incidence

= new cases occurring during a given time period × 10n

population at risk at start of time period/study

- ✓ It is a measure of the probability or risk of disease\
- ✓ Answer the question what proportion of the population will develop illness during the specified time period
- ✓ **Denominator** is the size of the population at the start of the time period/study
- ✓ **This measure is a proportion**, because all persons in the numerator are also in the denominator.
- ✓ Its synonyms are incidence proportion ,attack rate
- ✓ .

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Cumulative Incidence

The probability that an event will occur (if we calculated it during outbreak it is called Attack rate)

$$CI = \frac{\text{Number of new cases with disease in a specified time period}}{\text{Number of disease-free people at the start of the time period}}$$

Disease-free persons are Population at risk

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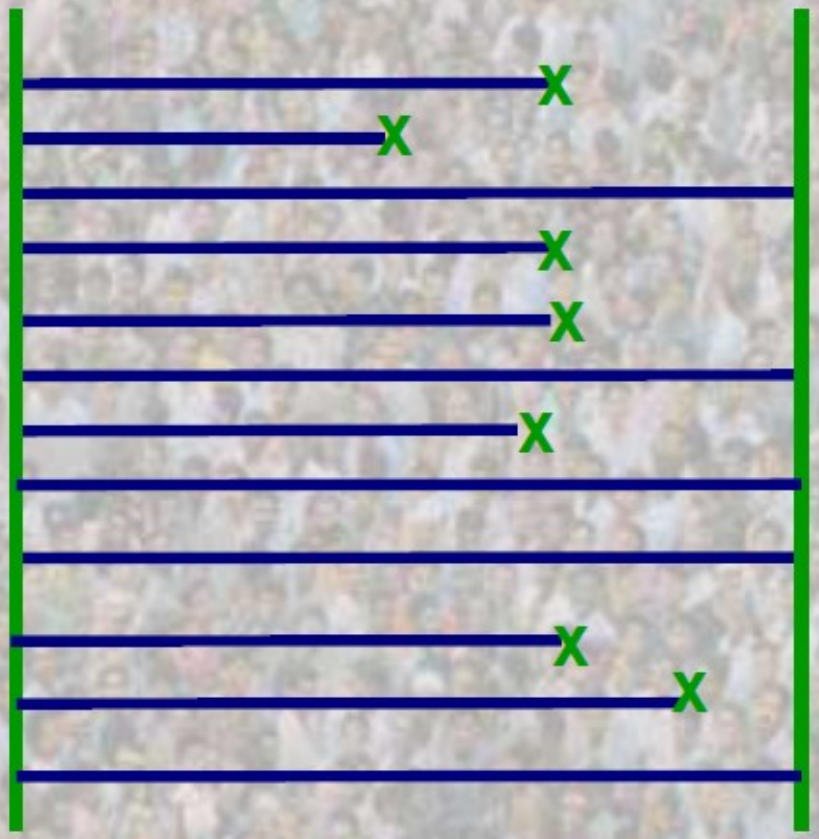
Cumulative Incidence

CI assumes that entire population at risk followed up for specified time period



Risk

CI = 7/12 per year

= 0.58 per year

x disease onset

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Cumulative incidence

Cumulative incidence(Risk)
=4/12 per year
=0.333 per year
Or 33.3% per year

X disease onset

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Example 3

- In a study of oral contraceptive (OC) use and bacteruria , a total of 2390 women aged 16 to 49 years were identified who were free from bacteruria . Of these, 482 were OC users at initial survey in1973. at second survey in 1976 , 27 of the OC user had developed bacteruria .

Q. calculate the cumulative incidence of bacteruria among OC user and show the appropriate steps

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Answer

Given

- ✓ **population at risk at start of study=482**
- ✓ **population who developed bacteruria=27**

Required

✓ **CI=?**

Solution

CI= total pupulation who develop bacterurai in a given period/population at risk

27/482 x100= 5.6%

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Attack Rate

- ✓ An attack rate is a variant of an incidence rate, applied to a narrowly defined population observed for a limited time, such as during an epidemic.
- ✓ expressed as a percent, so 10n equals 100.

$$\text{Attack rate} = \frac{\text{Number of new cases among the population during the period}}{\text{Population at risk at the beginning of the period}} \times 100$$

- ✓ It is a proportion—the persons in the numerator are also in the denominator.
- ✓ It is a measure of the **probability or risk of becoming a case.**

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Example

- Of 75 persons who attended the dinner of get together program , 46 subsequently developed gastroenteritis. Calculate attack rate

  x = Cases of GI= 46

  y = Number of persons at the program 75

  Then, the attack rate for gastroenteritis is = *46/75 × 100 = 61%*

✓ **In the** example above, among persons who attended the program, the probability of developing gastroenteritis was 61%, or the risk of developing gastroenteritis was 61%.

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Person-time Rate/incidence density

- ✓ A type of incidence rate that **directly incorporates time into the denominator.**
- ✓ Typically, **each person is observed from a set beginning point to an established end point** (onset of disease, death, migration out of the study, or end of the study).
- ✓ The **numerator is still the number of new cases,** but the denominator is a little different.
- ✓ The **denominator is the sum of the time each person is observed**
- ✓ **Person- time: is sum of length of time period passed free of illness (at risk) by each individual member of study**

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Person-time rate/incidence density

$$= \frac{\textit{Number of new cases during observation period} \times 10n}{\textit{Person-time at risk}}$$

- ✓ **For example, a person enrolled in a study who develops the disease of interest 5 years later contributes 5 person-years to the denominator.**
- *An individual followed for 10 years with out becoming a case, contributes 10 person-years*
- ✓ **A person who is disease-free at one year and who is then lost to follow-up contributes just that 1 person-year to the denominator.**
- ✓ Person-time rates are often used in cohort (follow-up) studies of diseases with long incubation or latency periods, such as some occupationally related diseases, AIDS, and chronic diseases.

Example

- In a cohort study, 600 people were followed over the course of 3 years as follows:
  - **100 persons for 1 year**
  - **200 persons for 2 years**
  - **300 persons for 3 years**
- *The no of person years of observation in this study is calculated as:*
  - **100 persons*1 year= 100 person-years**
  - **200 persons*2 years= 400 person-years**
  - **300 persons*3 years= 900 person-years**
  - **Total = 1400 person-years**

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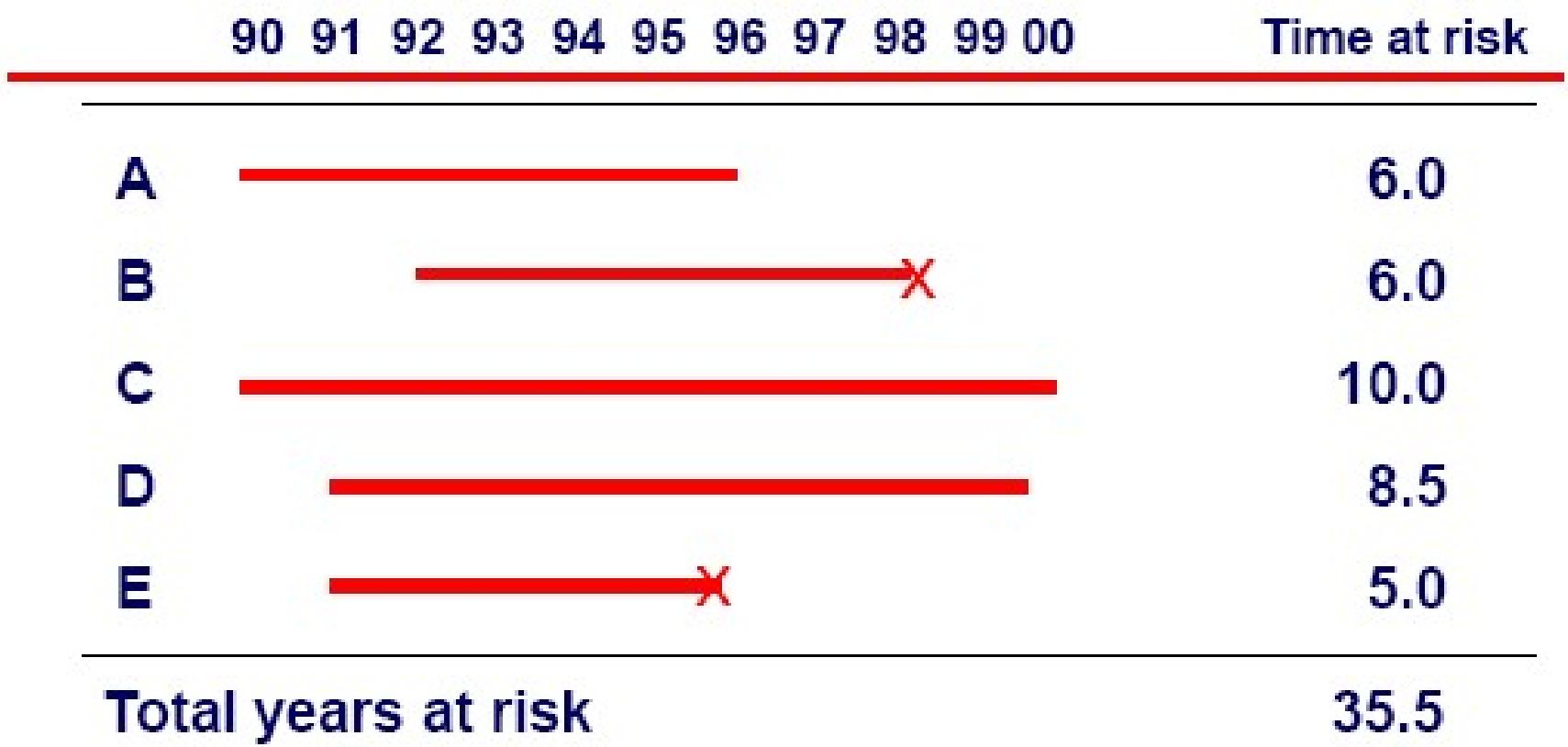

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Prevalence

$$\frac{\textit{all new and pre - existing cases during a given time period}}{\textit{population during the same time period}} \times 10^{n}$$

- ✓ It is proportion of a population affected by a disease at a given time.
- ✓ It is expressed as a percentage, per thousand, per hundred thousand

- ✓ Example : HIV/AIDS in X city in 1999:

Population 210,000

Cases 3,200

Prevalence 1.5%

- The value of 10n is usually 1 or 100 for common attributes. The value of 10n may be 1,000, 100,000, or even 1,000,000 for rare traits

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Prevalence:

$$\frac{\text{Number of cases of a disease at a specific time X K}}{\text{Total no of people present in that population at that time}}$$

- Mid-year population or average population can be used to estimate total population(denominator)
- Point prevalence: prevalence of disease at a point in time
- Period prevalence: how many persons are affected at any time during a certain period, such as during a single calendar year

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Prevalence…

- If we want to know how much disease is present over a longer period of time, period prevalence would be preferred.
- Mid year(Average) population is calculated

$$\frac{\text{Total Population at the begining} + \text{Total population at the End}}{2}$$

- The denominator for
  - Period prevalence: mid year(average) population
  - Point prevalence: total population at that time

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Point prevalence

- ✓ It is **proportion of a population** that is **affected by disease** at a **given point in time.**
- ✓ The **numerator** in point prevalence is **the number of persons with a particular disease or attribute on a particular date/week/month/year.**
- ✓ **It answers how much of a particular disease is present in a population at a single point in time**—to get a kind of **"stop action" or "snapshot"** look at the population with regard to that disease.

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Point prevalence

- ✓ Is **not an incidence rate, because the numerator includes pre-existing cases.**
- ✓ **it is a proportion,** because the persons in the numerator are also in the denominator.

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Period prevalence

- ✓ Answer the question **how much of a particular disease is present in a population over a longer period.**
- ✓ **The numerator** in period prevalence is **the number of persons who had a particular disease or attribute at any time during a particular interval.**
- ✓ **The interval** can be a week, month, year, decade, or **any other specified time period.**

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Example

- Two surveys were done of the same community 12 months apart. Of 5,000 people surveyed the first time, 25 had antibodies to histoplasmosis. Twelve months later, 35 had antibodies, including the original 25. We will calculate the prevalence at the first and second survey, and compare the prevalence with the 1-year cumulative incidence.

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Answers

1. Point Prevalence at the first survey:

x = antibody positive at first survey = 25

y = population = 5,000

x/y × 10n = 25/5,000 × 1,000 = 5 per 1,000

2. Period Prevalence at the second survey:

x = antibody positive at second survey = 35

y = population = 5,000

x/y × 10n = 35/5,000 × 1,000 = 7 per 1,000

2. Incidence during the 12-month period:

x = number of new positives during the 12-month period = 35 – 25 = 10

y = population at risk = 5,000 – 25 = 4,975

x/y × 10n = 10/4,975 × 1,000 = 2 per 1,000

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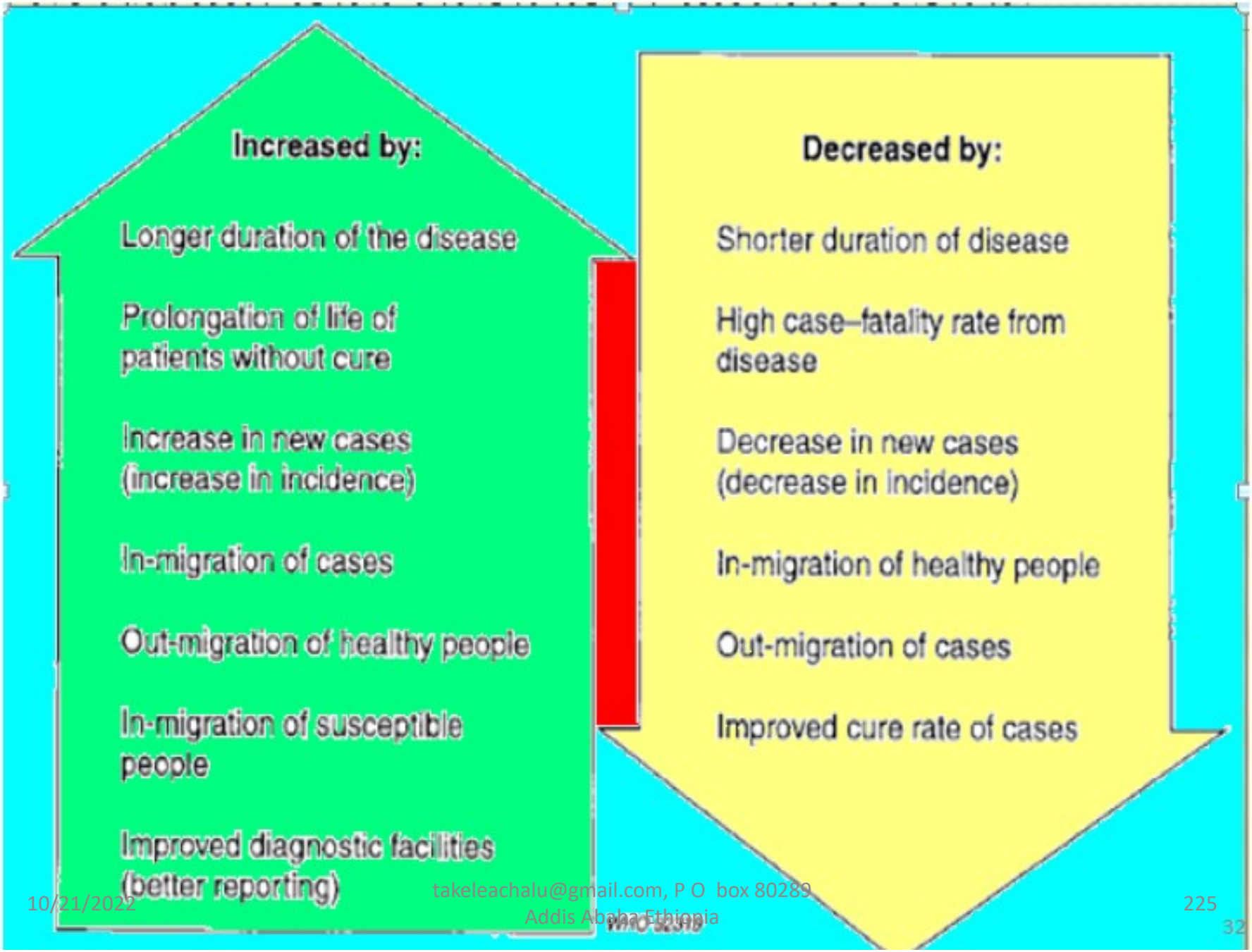
Prevalence


Increased by:
Longer duration of the disease
Prolongation of life of patients without cure
Increase in new cases (increase in incidence)
In-migration of cases
Out-migration of healthy people
In-migration of susceptible people
Improved diagnostic facilities (better reporting)
Decreased by:
Shorter duration of disease
High case–fatality rate from disease
Decrease in new cases (decrease in incidence)
In-migration of healthy people
Out-migration of cases
Improved cure rate of cases

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Home work (10%)

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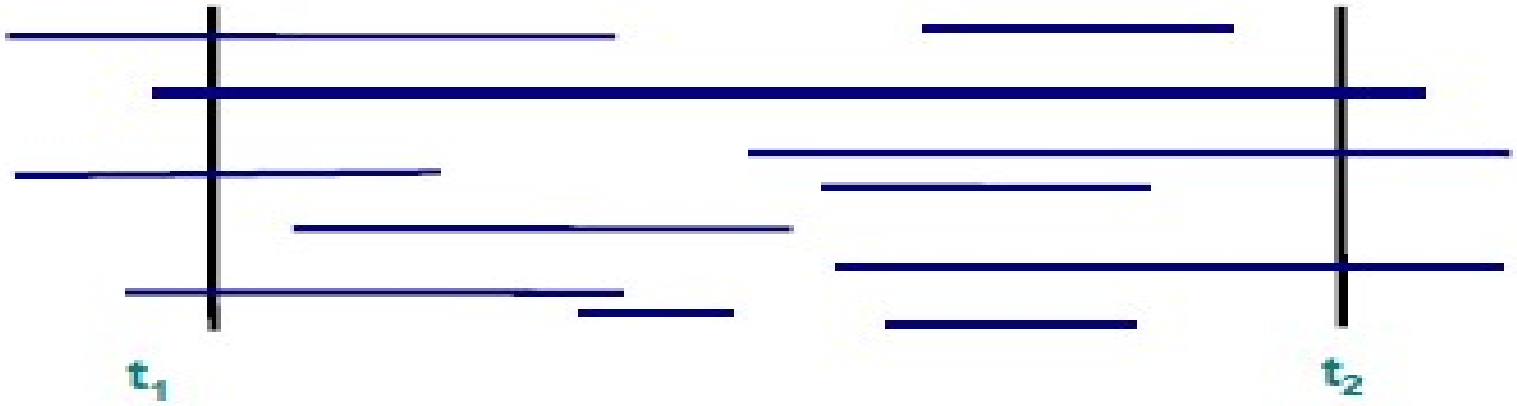
Q1(2.5%)

Example

A total of 100 people were at risk of disease x, which has no life time immunity.



What is the prevalence of disease X during time t_1?

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Q2(7.5%)

In the 1980s, 320 men provided blood specimens every 6 months as part of a hepatitis B vaccine study. These specimens were later tested for antibody to HIV. Of the 320, 300 were HIV-Ab-negative on all specimens, 20 were Ab-positive on all specimens, and finally 138 who were initially seronegative became positive in all specimen . Of those who were seropositive at the end of the study, 41 met the case definition for acquired immunodeficiency syndrome (AIDS). Do the next questions and show your work

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Questions

1. What is the prevalence of seropositivity among this cohort of men at the beginning of the study?
2. What is the prevalence of seropositivity among this cohort of men at the end of the study?
3. What is the incidence of infection during the study?
4. What is the incidence of AIDS during the study?
5. What proportion of seropositive persons developed AIDS?

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1.4. Current Drug Approval Process

- The current drug approval process includes:

1. **Preclinical phase-** animal testing
2. **Clinical Phase I-** metabolism of the drug, safe dosage range in humans, on Healthy subjects
3. **Phase II-** pharmacokinetics of the drug, common ADRs on the possible efficacy of the drug, daily dosage and regimen, on patient subjects
4. **Phase III -** evaluate a drug's efficacy, more information on toxicity, on patient subjects (500-3000)
5. **Phase IV –** post marketing surveillance

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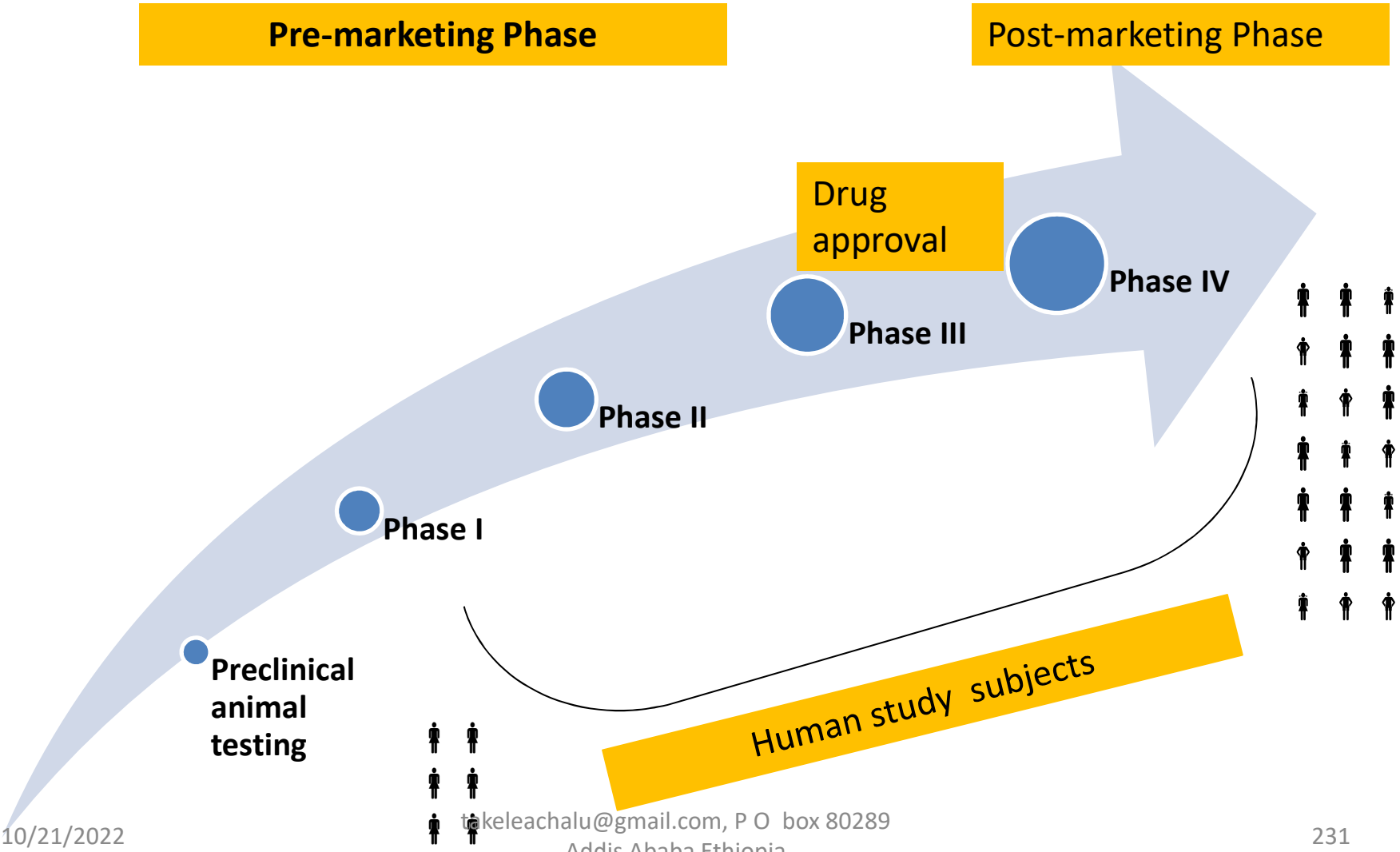
1.4. Current drug approval process (2)



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Limitations of Pre-marketing Trials

- Carefully selected subjects may not reflect real-life patients in whom drug will be used
- Study subjects may receive better care than real-life patients
- Short duration of treatment
- Study size
  - Studies with 3000 patients cannot reliably detect adverse events with an incidence of < 1 per 1000, even if severe
  - Studies with 500 patients cannot reliably detect adverse events with an incidence of < 1 per 166, even if severe

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Consequences of Limitations of Pre-marketing Trials

- About **20% of drugs** get new **"black box" warnings** after marketing
- About **4% of drugs** are ultimately **withdrawn** for safety reasons

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2. Study Designs Available for Pharmacoepidemiology Studies

Outline

2.1. Overview of the Scientific Method

2.2. Types of Association Between Factors Under Study

2.3. Types of Errors That One Can Make in Performing a Study

2.4. Criteria for the Causal Nature of an Association

2.5. Types of Epidemiologic Study Designs

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2.1. Overview of the Scientific Method

- **The whole point of science is to *UNCOVER THE TRUTH***
- **Two tools to peruse scientific inquiry are**
  1. **Our senses – through which we experience the world and make observations**
  2. **Our ability to reason – which enables us to make logical inferences**

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Scientific Method…

- **In science we impose logic on observations**
- **There are two kinds of logic we impose:**
  - **Deductive inferences:**
    - from the **general** (theory) to the **specific**, of the observations
    - Involving inferences from general principles
  - **Inductive inferences:**
    - Also called **logic of reasoning**
    - From **specific** to the **general**.
    - Proceeding from particular facts to a general conclusion
      - We make many observations
      - discern a pattern,
      - make generalizations, and
      - infer an explanation

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Scientific Method…

The scientific methods from the perspective of inductive approach is a three-stage process

1st stage: one studies a sample of study participants

2nd stage: one generalizes the information obtained from this sample of study participants

- **Drawing a conclusion** about a population in general

→ **an association**

3rd stage: one **establishes causation**

→ making inferences

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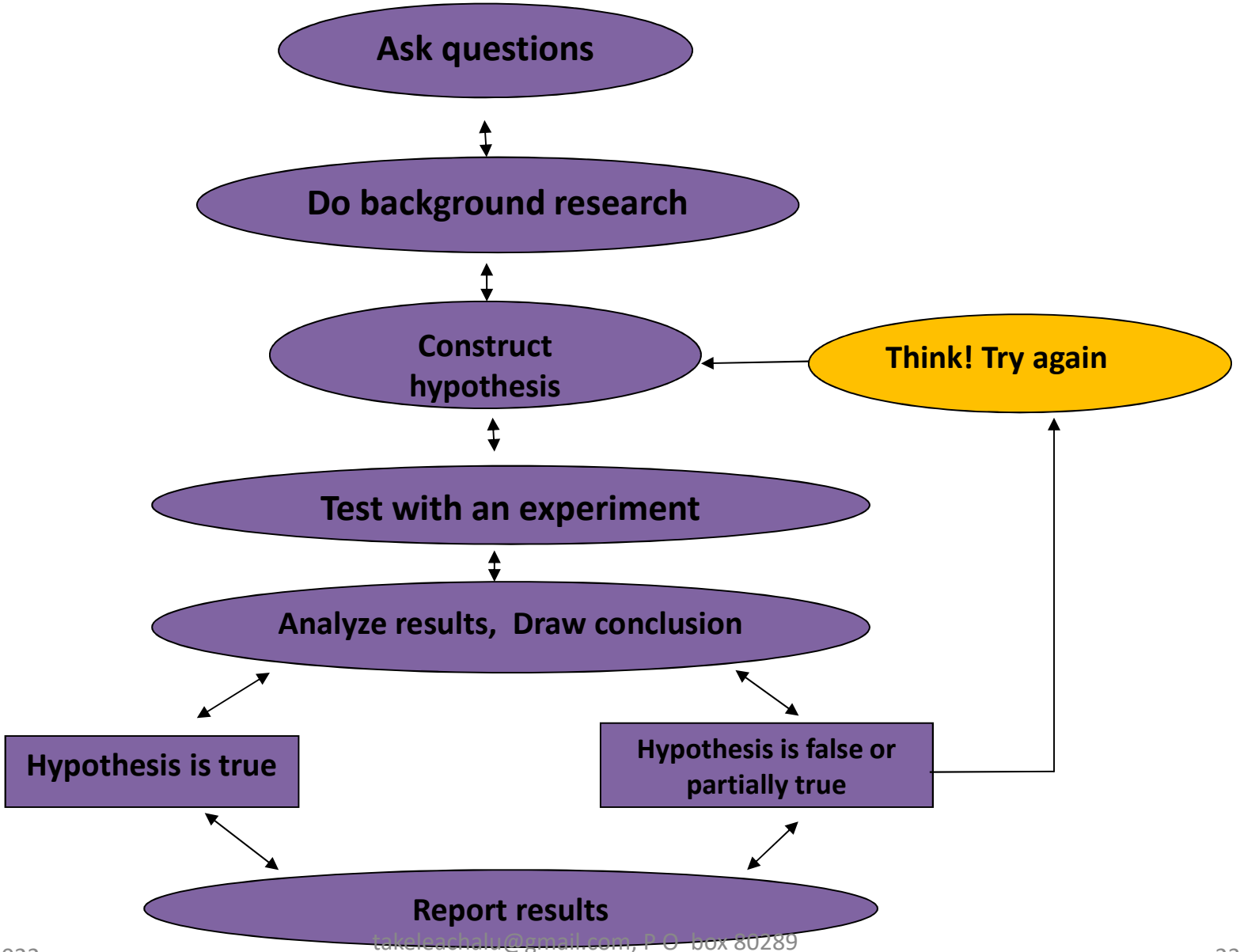
Inductive Research Framework



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2.2. Types of association between factors under study

There are **four basic types of associations** that can be observed in a study:

1. **No association** (independent)
2. **Artefactual association** (Spurious or False)
   a. Chance (Unsystematic Variation)
   b. Bias (Systematic Variation)
3. **Indirect** (Confounded Association)
4. **Causal association** (**Direct** or true)

- The basic purpose of research is to **differentiate among these types of association.**

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Hypothesis testing

- Establishing associations requires **hypothesis testing**
- There are two types of hypothesis in the scientific investigation:
  - **Null hypothesis** and
  - **Alternative hypothesis**
- The hypothesis we test statistically is called the **null hypothesis**

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Hypothesis testing

- **Example:** suppose we are testing the efficacy of a new drug on patients with **myocardial infraction**
  1. We divide the patients in to two groups: **Drug and No drug**

  2. **Measure mortality** in the two groups

  3. We say our hypothesis
     - that the drug makes no difference and
     - what we hope to do is to reject the 'no difference' hypothesis, based on evidence from our sample patients

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4. We specify our test hypothesis as follows:

- **H_o (hypothesis):** death rate in group treated with Drug A = death rate in group treated with Drug B
  - » That is equivalent to say:

  Ho: death rate in group A – death rate in group B = 0

- We test this against an alternate hypothesis known as **H_A**,
  - » the difference in death rate between the two groups does not equal to 0

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- If the observed difference is sufficiently greater than zero difference,
    - we reject the null hypothesis.
- If we reject the null hypothesis of no difference,
    - we accept the alternate hypothesis
- We can never be certain that
    - we are right in either **accepting or rejecting** a hypothesis
    - because of errors that can be produced in a study

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2.3. Types of errors that one can make in performing a study

There are three possible types of errors that can be produced in a study:

1. **Chance or random error**
   - Type I (alpha) error
   - Type II (beta) error
2. **Bias**
3. **Confounding**

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Chance or random error

- The purpose of statistical testing in science is to
  - **Evaluate the role of chance** and
  - **Estimate the probability** that the result observed in a study could have happened **purely by chance**
- The hypothesis we test statistically is called **the null hypothesis**
- The two kinds of errors:
  - Rejecting the null or test hypothesis incorrectly– **Type I error**
  - Fail to reject null hypothesis incorrectly – **Type II error**

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Consider the hypothesis below:

- **Null hypothesis**: drug has no effect ↔ no difference in mortality between patients using drug and not using drug

- **Alternate hypothesis**: Drug has effect ↔ reduces mortality

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Decision on the basis of the sample	True state of nature: H_o true	True state of nature: H_A true
Reject H_o	**Type I error**	No error
Do not reject H_o	No error	**Type II error**

- **If we reject H_o** and accept H_A, we conclude that there is relationship between drug and mortality
- **If we don't reject H_o**, we conclude that there is no relationship between drug and mortality.

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Actions to be taken based on decisions:

1. If we reject null hypothesis in favor of the alternative hypothesis we will use the drug

   → **Consequence of wrong decision**: type I error. **We will use the drug but the patient don't benefit.**

   Presuming the drug is not harmful in itself,

   - we do not directly hurt the patients
   - but since we think that we have found the cure,
   - we may no longer test other drugs

2. If we believe the null hypothesis (i.e., fail to reject it) we will not use the drug

   →**Consequence of wrong decision**: type II error.

   - Since in reality the drug is beneficial, by withholding it,
   - we will allow patients to die who might otherwise have survived.

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- We cannot eliminate the risk of making one of these types of errors
  - but can lower the probabilities that we will make these errors
- The probability of making a type I error is known as **the significance level of a statistical test**

- To lower the probabilities of both the **type I and Type II error in a study**
  - it is necessary **to increase the number of observations**

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Confidence interval and p – value

- Two options to answer whether an observed association in a sample is large enough to be evidence of a true association in the population from which the sample was drawn.
    - The 95% confidence interval
    - P value
- A 95% confidence interval gives a plausible range of values that should contain the true association in the population.

- A P-value is the probability of getting the observed association, or more extreme, in the sample purely by chance from a population where the **true association is one.**

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Bias (systematic variation)

- Bias refers to any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposures effect on the risk of disease

- **Systematic variation in a consistent manner in which two study groups are treated or evaluated differently**
- This consistent difference
  - can create an apparent association where one actually does not exist
  - It also **masks true association**

- Biases once present cannot be corrected
- They represent errors in the study design
- **Proper study design** is the only protection against biases

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- Two main types of bias
  1. **Selection bias**
     - Errors in the process of selecting the study population
     - Factors that influence study participation
  2. **Information bias**
     - occurs during data collection.
     - Errors in the way the information is collected
     - **Some Types and Sources of Information Bias**
       - Bias in abstracting records
       - Bias in interviewing
       - Bias from surrogate (substitute or proxy) interviews
       - Surveillance bias
       - Recall bias
       - Reporting bias

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Selection Bias

- Occurs when selection of cases or control is related to exposure
  - Selection of patients from hospitals, specialised centres
  - Selection of “healthy” controls from hospitals
  - Response rate bias
  - Self selection bias
  - Survival bias

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Information Bias

- Misclassification
- Observer Bias
- Recall Bias

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Information Bias – Observer Bias

- Observer know the underlying hypothesis and ask more probing question to those exposed than controls
- Remedies for observer bias
  - Blind the observer
  - Use highly structured interview

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Information Bias - Recall Bias

- Disease status affect patients' response
  - Patient with musculoskeletal diseases are more likely to remember minor trauma
- Particular problem with case control studies
- Remedies for recall bias
  - Find reliable records
  - Use control with other illnesses

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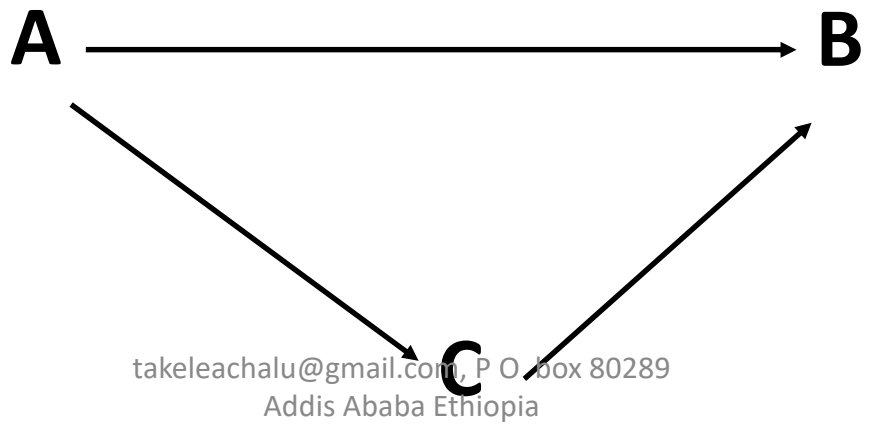
Confounding

- Confounding refers to the **mixing of the effect of an extraneous variable** with the effects of the **exposure** and **disease** of interest.
- It arises when some causes other than the exposure under study is more, or less, prevalent in the exposed group than in the unexposed.
- Such variable is defined as an **extraneous (third) variable** which is associated with the exposure and, independent of that exposure, be a risk factor for the disease.



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- **Example**
  - The RR is determined from an observational study
  - This raises the question
    - whether the exposed and the reference groups are similar in all respects except the exposure under study

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- In addition to the two principal factors, which determine the RR, namely the outcome of the adverse event and the drug exposure status,
  - We must also consider tertiary factors of potentially large importance
  - These factors are related to both the outcome and exposure status – confounding factors
  - Example: See table I and II next slide

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Table I. Data from a cohort study by Careson et al. (1987) on the effects of NSAIDs on the risk of UGIB	
Exposed to NSAIDs	
No. of cases of UGIB	155
Person-months	1220000
Rate of UGIB/10000 person - months	1.27
Not exposed to NSAIDs	
No. of cases of UGIB	96
Person-months	1157000
Rate of UGIB/10000 persons-months	0.83
Rate ratio	1.5

Table 2. Hypothesis stratification to illustrate confounding by alcohol consumption of data by Careson et al. (1987) on the effects of NSAIDs on the risk of UGIB

Exposed to NSAIDs	Alcohol consumption	
	Heavy	Light
Exposed to NSAIDs		
No. of cases of UGIB	143	12
Person-months	492000	728000
Rate of UGIB/10000 person-month	**2.91**	**0.16**
Not exposed to NSAIDs		
No. of cases of UGIB	95	1
Person-months	982,000	175000
Rate of UGIB/10000 person-months	**0.97**	**0.06**
Rate ratio	3.0	2.9

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Characteristics of a confounding variable

1. Associated with the disease of interest in the absence of exposure.
   - risk factor for the study outcome among exposed group
   - risk factor for the study outcome among non exposed
2. **Associated with the study exposure** but not as a consequence of the exposure.

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Effect of confounding

1. **Totally or partially accounts** for the apparent effect

2. **Mask** an underlying true association

3. **Reverse** the actual direction of the association

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Remedies to Confounding

1. In the DESIGN confounding could minimize by:

- **Match** (match case and control for gender and age)
- **Restriction** (limit study to certain groups)
- **Randomisation** (limit to treatment)

2. ANALYSIS

- **Stratification**
- **Standardisation**
- **Statistical modelling (multivariate analysis)**

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Summary

- Probability of **random error** can be quantified using statistics.
- **Bias** needs to be prevented by designing the study properly and
- Confounding can be controlled in either the design of the study or in its analysis.

- If the **three types of errors** can be excluded, then one is left with a **True Causal Association**

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Measures of Association

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Exposure

- Exposure in usual sense,
  - Eg. Ingestion of contaminated food
  - Eg. Droplets from someone with active pulmonary tuberculosis
- Behaviors
  - Eg. Sharing needles, drinking alcohol, etc
- Treatment
  - Eg. Intervention , education program
- Trait
  - Eg. Genotype

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Outcome

- Disease
  - Eg. Malaria, TB
  - Eg. Diabetes
- Event
  - Eg. Injury from land mine, car accident
- Condition
  - Eg. Blindness
- Death
- Other

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Learning Objectives

- List common measures of **association and measures of public health impact**
- Calculate and interpret ***risk ratio*** **and** ***odds ratio*** and describe their use
- Calculate and interpret ***attributable risk percent*** and ***vaccine efficacy***

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Association

Exposure ⟷ **Outcome**

Is there a relationship between the exposure and outcome of interest?

What kind?
How strong?

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Definition—

Association

~ is statistical relationship between two or more variables

~ requires comparing two groups:

- Exposed Vs Unexposed
- With outcome Vs Without Outcome

What possible Questions we may ask?

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Question—

Q: is there Ă?

Q: is the Ă true?

Q: if not true what could it be?

Q: How do we express association?

Q: How do we measure?

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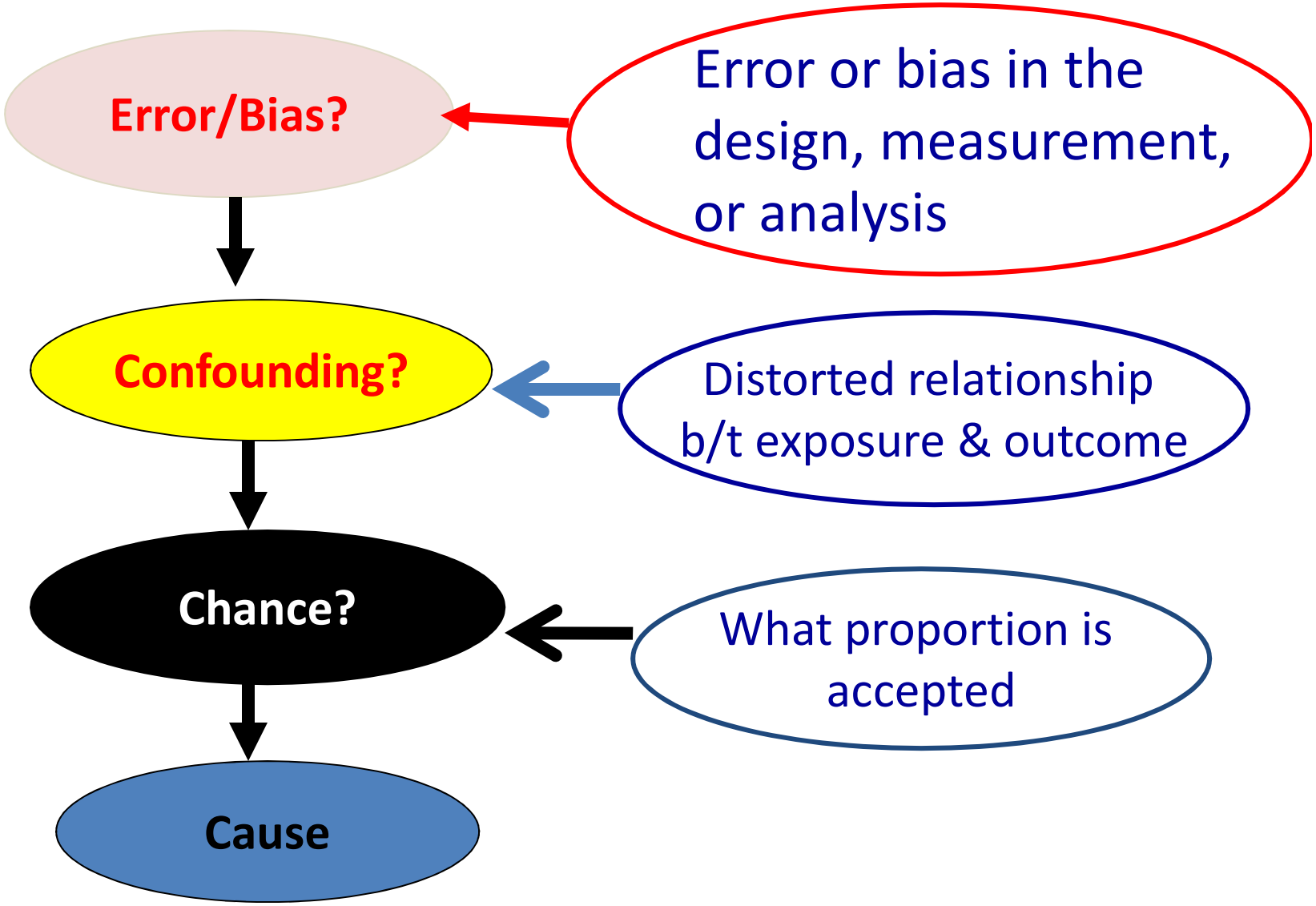
Relationship/Association can be due to



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Measures of Association

Relative risk (Risk Ratio) (RR)

PROSPECTIVE, EXPERIMENTAL STUDIES

Odds Ratio (OR)

CASE CONTROL, CROSS-SECTIONAL STUDIES

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How do we describe association or relation?

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Description of Association

- Variables can be ***Related*** or ***Unrelated*** to one another

- If the two variables are ***Related***, they can be related either:

  1. **Direction *positively*** or ***negatively***
  2. **Strength*: strongly*** or ***weakly*** (one variable can have *large* or *small effect* on the other)
  3. **Significance*: significantly*** or ***not significantly***

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Significance—
Statistically Significant or Not?

- Statistically significant

  ➔ association is unlikely to be due to chance

But remember:

  – It is dependent on the strength of the association and sample size

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Why? (Cont…)

Exposure ⟷ Outcome

- Is there a relationship between the exposure and outcome of interest?

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Association

- Statistical relationship between two or more variables.
- Probability of occurrence of an outcome depends on,
  - Presence of one or more characteristics
  - Occurrence of one or more events
  - Quantity of one or more other variables

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Measures of Association

- Epidemiologic Measure of Association
  - Quantifies or expresses the strength of the relationship between an "exposure" and “outcome” of interest
  - Quantifies the difference in occurrence of disease or death between two groups of people who differ on "exposure“

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(Cont…)

- Types of measures of association and Impact
  - Relative Risk (RR) or Risk Ratio,
  - Odds Ratio (OR) or Cross Product Ratio,
  - Attributable Risk (AR),
  - Attributable Risk Percent (AR%)
  - Population Attributable Risk (PAR)
  - Population Attributable Risk Percent (PAR%)

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Standard Two-by-Two Table

- It is also called *Contingency Table*
- The 2X2 table provides a standard and simplified way of data presentation for calculating measures of association.
- Almost all epidemiologic studies can be summarized in a 2 X 2 table.

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2X2 (Cont…)

		Outcome		Total
		Diseased (D+)	Not Diseased (D-)	
Exposure	Exposed (E+)	a	b	a+b
	Not Exposed (E-)	c	d	c+d
	Total	a+c	b+d	a+b+c+d

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Cont…

a = number of individuals who are exposed and have the disease

b = number who are exposed and do not have the disease

c = number who are not exposed and have the disease

d = number who are both non-exposed and non-diseased

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Risk

- It is a measure of probability of getting a disease.

$$\text{Risk} = \frac{\text{Number of new cases during a specified period}}{\text{population at risk during the specifed period}}$$

- It is also called as:
  - "**Attack Rate**"
  - **Risk of Disease**
  - **Cumulative Incidence**
  - **Incidence Proportion**

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Relative Risk (RR)

- Relative Risk indicates the likelihood of developing the disease in the exposed group relative to non-exposed.
- Measure of association between incidence of disease and factor being investigated
- Ratio of cumulative incidence among exposed and non exposed persons
- It is commonly used in Cohort Studies.
- It is given by :-

$$RR = \frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)} \qquad RR = \frac{R_e}{R_{\check{e}}}$$

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2X2 (Cont…)

		Outcome		Total
		Diseased (D+)	Not Diseased (D-)	
Exposure	Exposed (E+)	a	b	a+b
	Not Exposed (E-)	c	d	c+d
	Total	a+c	b+d	a+b+c+d

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Cont…

- If **RR** calculated from **cumulative incidence** it is called **Risk ratio** where as if it is calculated from **incidence rate** (**person units of time**) it is called **Rate ratio**

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Example: Cohort Study 2X2 Table

		Outcome (Death)		Total
		Infants Died	Infants Alive	
Mother's Education	Illiterate	579	4,442	5,021
	Literate	99	1,269	1,368
	Total	678	5,711	6,389

$$RR = \frac{\left(\frac{579}{579 + 4{,}442}\right)}{\left(\frac{99}{99 + 1269}\right)} = 1.59$$

infant of illiterate mother had 1.59 times higher risk of death compared to infant of literate mother.

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Example 1

	Breast Cancer	No Breast Cancer	Total
Alcohol	70	2,930	3,000
No alcohol	50	2,950	3,000

RR using Cumulative Incidence (CI):

$$= \frac{a/(a+b)}{c/(c+d)} = \frac{70 / 3{,}000}{50 / 3{,}000} = 1.4$$

Interpretation: women who drink alcohol are about 1.4 times at higher risk of developing breast cancer than who not drink alcohol

Exercise 1

- Imagine that the incidence of lung cancer is compared in two cities, one with polluted air (A), the other not (B).

- In the polluted city there were 20 cases in a population of 1000; in the other city 10 cases in a population of 1000.

1. *What is the relative risk of lung cancer in the polluted city (A)?*

2. *What is the relative risk of lung cancer in the less polluted city (B)?*

3. *What explanations are there for the higher relative risk in the polluted city?*

The two by two table: lung cancer as a common outcome

Risk factor	Outcome: lung cancer	Outcome: no lung cancer	total
Living in city A	a= 20	b=80	a+b=100
living in city B	c= 10	d= 90	c+d=100
total	a+c=30	b+d=170	a+b+c+d=200

1) Calculate risk of lung cancer among exposed
2) Calculate the risk of lung cancer unexposed
3) Calculate the relative risk of lung cancer among exposed

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Example:

Age at 1st birth	Breast cancer Yes	No	Total
≥25 yrs	31	1597	1628
< 25 yrs	65	4475	4540
Total	96	6072	6168

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

$RR = R_e/R_{\grave{e}}$

Risk in ≥ 25 years = a/a+b = 31/1628 = 0.019

Risk in <25 years = c/c+d = 65/4540 = 0.014

RR = 0.019/0.014 = 1.36

Women who first gave birth at an older age are 36% more likely to develop BC.

Is this increase significant *or* just chance*?*

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Rate Ratio

- **compares two groups in terms of incidence rates, person-time rates, or mortality** rate
- Like the risk ratio, the two groups are typically differentiated by demographic factors or by exposure to a suspected causative agent.
- The rate for the group of primary interest is divided by the rate for the comparison group.
- Rate ratio = $\frac{\textit{rate for comparison group}}{\textit{rate for group of primary interest}}$
- The interpretation of the value of a rate ratio is similar to that of the risk ratio.

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Death rates and rate ratios from lung cancer by daily cigarette consumption, Doll and Hill physician follow-up study, 1951-1961

	Death rates	
Cigarettes per day	per 1000 per year	Rate ratio
0 (Nonsmokers)	0.07	—
1-14	0.57	_____
15-24	1.39	_____
25+	2.27	_____

- Rate ratio = 0.57 / 0.07 = 8.1
- The rate of lung cancer among smokers of 1-14 cigarettes is 8.1 times higher than the rate of lung cancer in nonsmoker
- Calculate for 15-24, 25+=19.85 & 32.4 respectively

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Presentation of data from cohort study with person time unit denominator

	Disease		Person-time units
	Yes	No	
Exposure Yes	a	—	PY_1
Exposure No	c	—	PY_0
Total	$a + c$		$PY_1 + PY_0$

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1. Incidence (density) rate

Rate ratio

- **Denominator = "Peron-time" unit**

Ex: Rate ratio in ENARP cohort

HIV status	Number dev TB	PY observed	Incidence Rate/1000 PYO	Rate ratio
Negative	14	2054		
Positive	10	222		

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Incidence rate cont'd…

Rate ratio in ENARP cohort

HIV status	Number dev TB	PY observed	Incidence Rate/1000 PYO	Rate ratio
Negative	14	2054	6.8	0.15
Positive	10	222	45.0	6.62

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Risk Ratio / Relative Risk

$$\frac{\text{Risk in "exposed" group}}{\text{Risk in "unexposed" group}}$$

EXAMPLE 1:

Relative risk of death among diabetic men vs. non-diabetic men

$$RR = \frac{100/189}{811/3151} = \frac{0.529}{0.257} = \frac{52.9\%}{25.7\%} = 2.1$$

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Incidence Risk cont'd…

Ex: Risk ratio in Jimma Birth Cohort

ANC attendance	Number of infants	Number of death	IMR/1000	Risk ratio
Yes	4262	354	83.1	0.68
No	4011	493	122.9	1.14

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Exercise RR

Contact with CSW	HIV: Yes (+)	HIV: No (-)	
Yes (+)	20	40	60
No (-)	10	60	70
	30	100	130

$$RR = \frac{20/60}{10/70} = 2.33$$

The risk of HIV infection among people having contact with CSW is about 2.33 times that of people having no contact

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Interpretation of RR

- The value of RR ranges b/t **0** and **infinity**
- RR is always a **positive number**
- **RR = 1**
  - **no association** b/t the risk factor (independent variables) & the outcome (dependent variables)
  - i.e., the risk of acquiring the disease is the same for those subjects with the risk factor and without the risk factor

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Incidence rate cont'd…

Rate ratio in ENARP cohort

HIV status	Number dev TB	PY observed	Incidence Rate/1000 PYO	Rate ratio
Negative	14	2054	6.8	0.2
Positive	10	222	45.0	6.62

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Incidence rate cont'd…

Denominator = "Person-time at- risk" unit

Smoking status	Number diseased	PY observed	Incidence Rate/1000 PYO	Rate ratio
Negative	359	32145.4	11.17	0.52
Positive	484	22713.3	21.31	1.9

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Interpretation cont'd…

- **RR=/=1, there is an association**
- **RR > 1** indicates that the risk of acquiring the disease is greater among subjects with the risk factor than subjects among without the risk factor
- **RR < 1** indicates the risk of acquiring the disease is less among subjects with the risk factor than among subjects without the risk factor
  - Suggests that the factor exposure may be protective
    - i.e. exposure associated with decreased risk (in case in randomized controlled trial)

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Interpretation cont'd…

- **RR** comes nearer to 1 (nullifying point), then the association is said to be a **weak association**

  - The further away from 1, the stronger the association between exposure and disease

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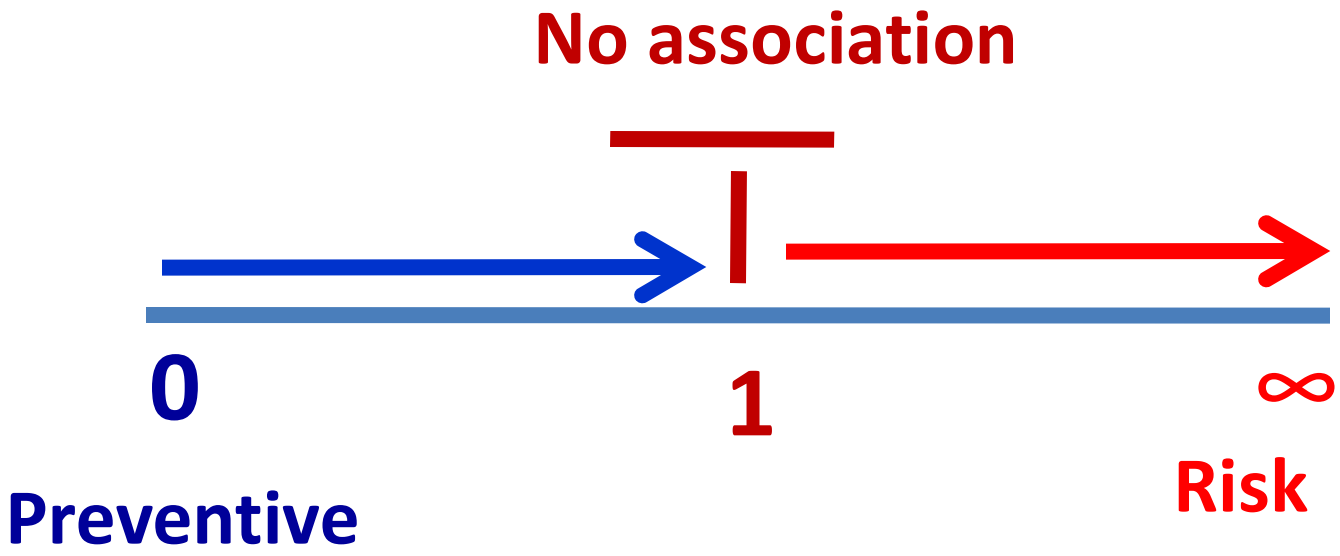
Interpretation of Relative Risk

In general the strength of association can be considered

1. If RR=1, no association between exposure and disease
   - Incidence rates are identical between groups
2. If RR > 1 = Positive association
   - Weak, if RR b/n 1.2-1.4
   - Moderate, if RR b/n 1.5-2.9
   - High, if RR >3
3. If RR< 1 = Negative association or protective effect

Interpretation cont'd…



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Relative Risk: Example (Cohort Study)

Example: Birth Cohort

ANC Attendance	Number of Infants	Number of deaths	IMR per 1000	Risk Ratio
Yes	4262	354		
No	4011	493		

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Example: Cohort Study (Cont…)

Example: Birth Cohort

ANC Attendance	Number of Infants	Number of deaths	IMR per 1000	Risk Ratio
Yes	4262	354	83.1	
No	4011	493	122.9	

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Example: Cohort Study (Cont…)

Example: Birth Cohort

ANC Attendance	Number of Infants	Number of Deaths	IMR per 1000	Risk Ratio
Yes	4262	354	83.1	1.00
No	4011	493	122.9	1.48

$$\mathbf{RR} = \frac{122.9}{83.1} = \mathbf{1.48}$$

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Odds Ratio (OR)

- In statistics, an odds of an event is the ratio of the probability that the event WILL occur to the probability that the event will NOT occur
  - Eg. In 100 births, the probability of a delivery being a boy is 51% and being a girl is 49%. The odds of a delivery being a boy is 51/49 = 1.04
- The term odds ratio is a description for one set of odds divided by another odds.

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OR cont'd…

- For example suppose the probability of the rain in the next hour is 80%.
- Then the probability of no rain in the next hour is 100-80=20%, so the odds in favor of rain is 0.8/0.2 = 4.
- If a and c are very much smaller than b and d then RR is approximated by OR = ad/bc
- RR can be estimated by OR if the following conditions are fulfilled

1. The controls are representative of the general population
2. The selected cases are representative of all cases
3. The disease is rare

OR (Cont…)

- In the epidemiological context, the *odds* are the chances of :

1. being exposed as opposed to not being exposed

OR

2. being diseased as opposed to not being diseased.

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$$OR = \frac{\text{Odds of positive outcome among cases}}{\text{Odds of positive outcome among controls}}$$

Odds of exposure among cases **(a/c)** O_e .

Odds of exposure among controls **(b/d)**

$O_{\grave{e}}$

$$\frac{\text{occurrence of exposure among cases}}{\text{non-occurrence of exposure among cases}}$$

$$\frac{\text{occurrence of exposure among control}}{\text{non-occurrence of exposure among control}}$$

OR = $O_e / O_{\grave{e}}$ =

ad/bc

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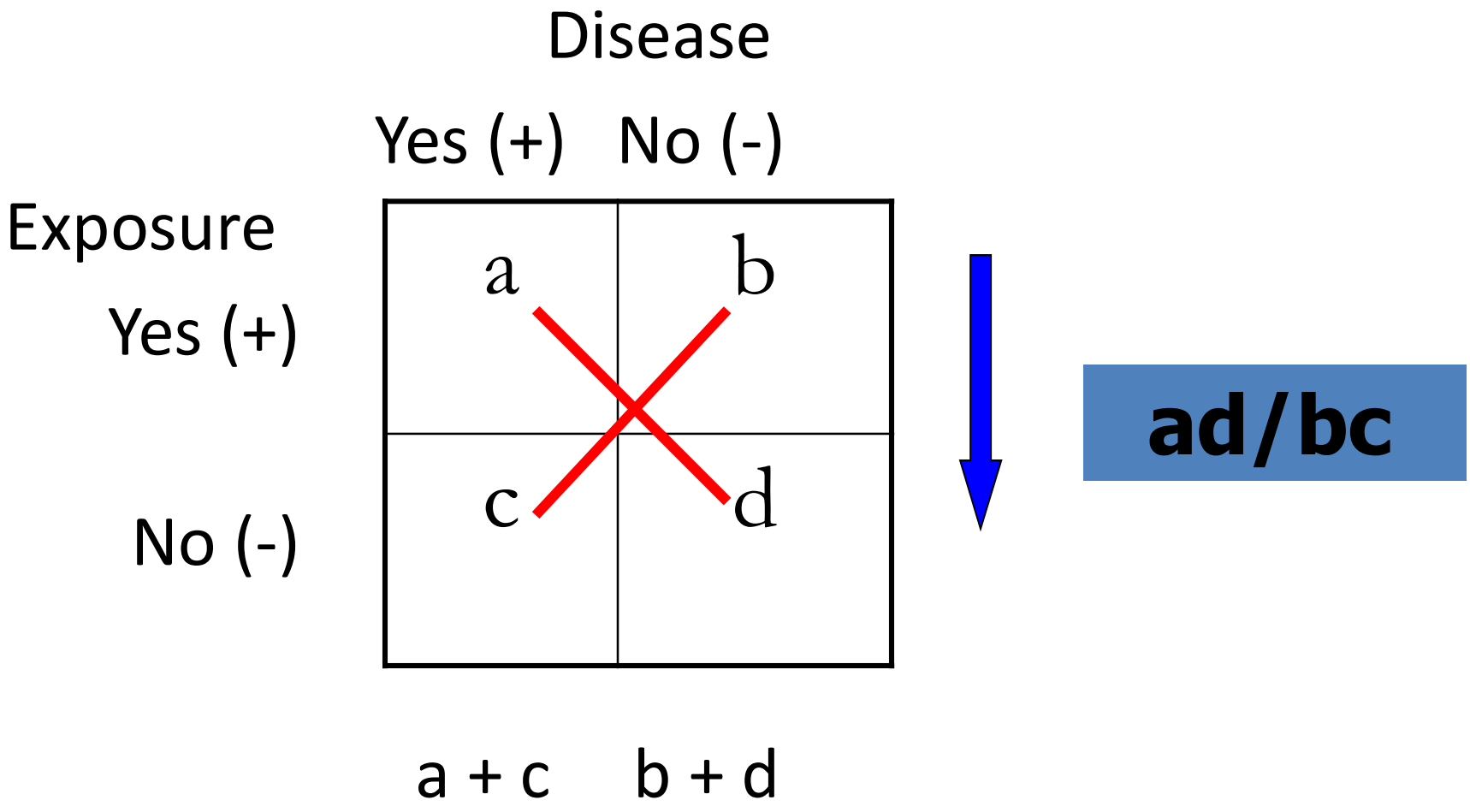
OR is a cross product



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OR (Cont…)

In a standard 2X2 table,

- The odds of exposure to the risk factor for the group with the disease are the (***a/c)*** and for the group without the disease, ***(b/d)***.
- The odds ratio for exposure is simply the odds ***a/c*** divided by the odds ***b/d***.
- Similarly, the odds of the disease in those exposed to the risk factor are ***a/b***, and for those not exposed are ***c/d***.

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OR (Cont…)

- In the exposure-disease 2x2 table, the odds of having a disease in the exposed group is the same as the odds that an exposed person develops the disease

$$\textbf{Exposure Odds Ratio (OR)} = \frac{(a/c)}{(b/d)} \qquad \textbf{OR} = \frac{ad}{bc}$$

$$\textbf{Disease Odds Ratio (OR)} = \frac{(a/b)}{(c/d)}$$

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Cont…

- The odds ratio is sometimes called the **cross-product ratio, because the numerator is the product of cell *a and cell d, while the denominator is the*** product of cell *b and cell c.*
- *If we draw A line from cell **a** to cell **d** (for the numerator) and another from cell **b** to cell **c** (for the denominator) creates an x or cross on the two-by-two table.*

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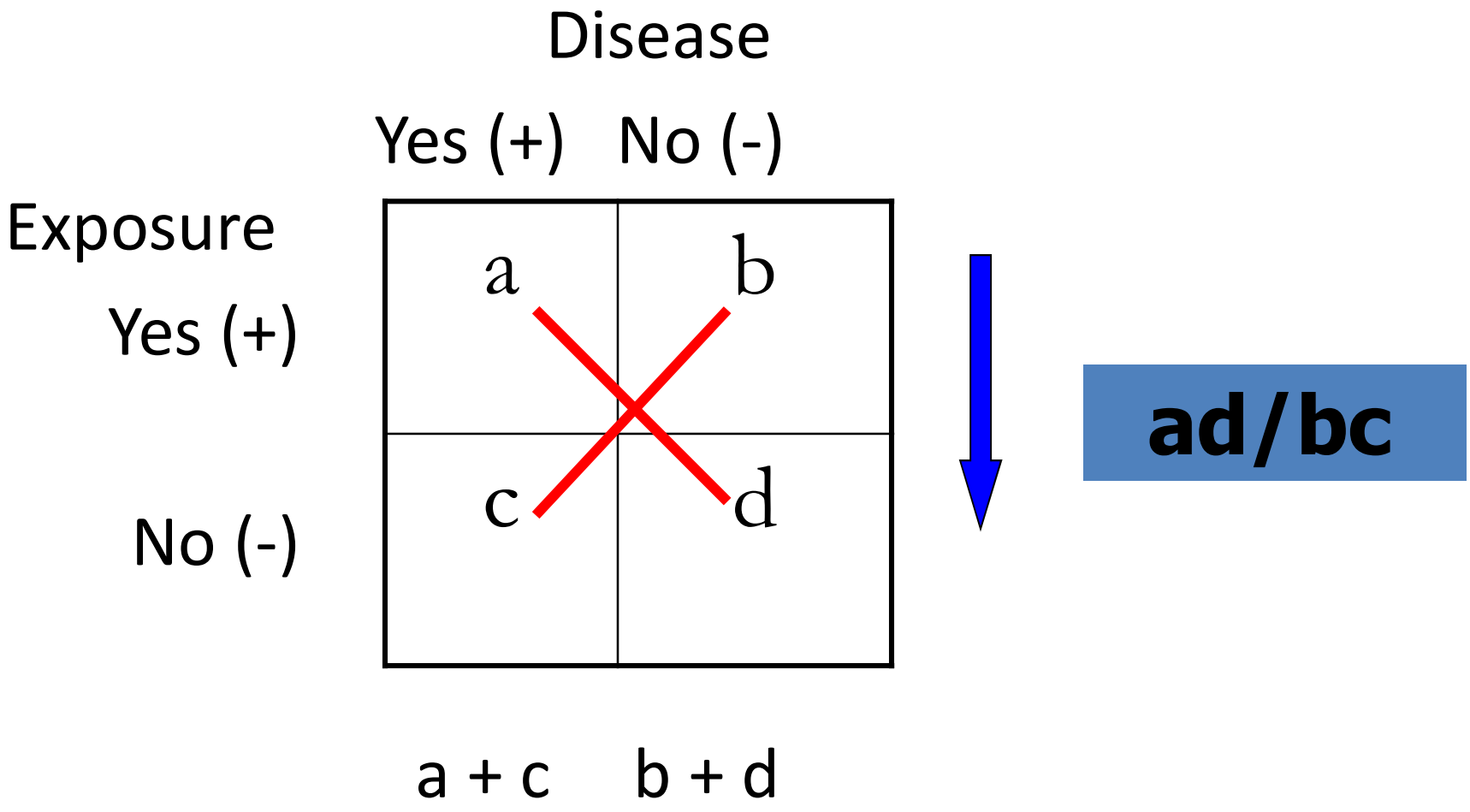
OR is a cross product



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B. For case-control

Odds ratio
= cross product ratio

- The **Odds** of disease is the probability that an individual experiences the disease as a function of exposure

- The ***odds ratio (OR)*** *is the odds in favor of* disease for the exposed group divided by the odds in favor of disease for the unexposed group

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$$OR = \frac{\text{Odds of positive outcome among cases}}{\text{Odds of positive outcome among controls}}$$

$$\frac{\textbf{Odds of exposure among cases}}{\textbf{Odds of exposure among controls}} \qquad \textbf{(a/c)} \qquad \frac{\textbf{(a/c)}}{\textbf{(b/d)}} \qquad \textbf{O}_e \textbf{ .}$$

$\textbf{O}_{\grave{e}}$

$$\frac{\text{occurrence of exposure among cases}}{\text{non-occurrence of exposure among cases}}$$

$$\frac{\text{occurrence of exposure among control}}{\text{non-occurrence of exposure among control}}$$

$$\textbf{OR} = \textbf{O}_e / \textbf{O}_{\grave{e}} = \textbf{ad/bc}$$

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Odds ratio

- An **indirect measure** of a risk in a **rarely** occurring diseases
- It is used in a **case-control** and **cross-sectional**
  - We can't directly estimate either RD or the RR

- Cases & controls are predetermined and we are calculating to determine whether cases or controls are more exposed to a postulated risk factor
  - Ex: Comparison b/t the No. of people having contact with CSW within the cases and No. of people having contact with CSW among the controls.

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Exercise OR

Condom use	HIV: Yes (+)	HIV: No (-)
Yes (+)	10	60
No (-)	20	40

$$RR = \frac{10*04}{20*60} = 0.33$$

The risk of HIV infection among people using condom is about 0.33 times that of people who didn't use condom or

condom users have about 67 % (1.00-0.33)* 100%) less likely to develop HIV compared to non-users

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Relationship b/t RR & OR

- Estimation technique, testing & CI construction are similar.
- In rare outcome (disease) i.e. the probability of getting the disease is small **OR ≈ RR**

- **RR** can be calculated **only from cohort** study, whereas an **OR** can be calculated from **both** cohort & case-control study.
- Neither **RR** nor **OR** gives any clue to the **magnitude of risk** in the background population or control group.

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	Breast Cancer	No Breast Cancer
Alcohol	70	100
No alcohol	50	140

$$OR = \frac{a \times d}{b \times c} = \frac{(70)\,(140)}{(50)\,(100)} = 2.0$$

Interpretation: women who are drinking alcohol had 2 times higher risk of developing breast cancer when compared to non dirking

NB: OR used for case control studies because persons are selected based on disease status so you can't calculate risk of getting disease

Example: of the “Rare Disease” assumption

	D+	D-	Total	Risk
E+	90	50	140	0.643
E-	10	50	60	0.167

$$\textbf{RR} = \frac{\textbf{90/140}}{\textbf{10/60}} = \frac{\textbf{0.643}}{\textbf{0.167}} = \textbf{3.9}$$

$$\textbf{OR} = \frac{\textbf{ad}}{\textbf{bc}} = \frac{\textbf{(90)(50)}}{\textbf{(50)(10)}} = \textbf{9.0}$$

Example cont'd…

	D+	D-	Total	Risk
E+	90	499,950	500,040	0.00018
E–	10	499,950	499,960	0.00002

$$\text{RR} = \frac{90/\ 500{,}040}{10/\ 499{,}960} = \frac{0.00018}{0.00002} = 9.0$$

$$\text{OR} = \frac{ad}{bc} = \frac{(90)(499{,}950)}{(499{,}950)(10)} = 9.0$$

Odds Ratio: Example (Cross-sectional Study)

Example: Women's Health & Life Events

Physical Violence	Poor Health	Good Health	Odds Ratio
Yes	677	424	
No	566	594	

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Example: Cross-sectional Study (Cont…)

Example: Women's Health & Life Events

Physical Violence	Poor Health	Good Health	Odds Ratio
Yes	677	424	1.68
No	566	594	1.00

$$OR = \frac{677 \text{ X } 594}{424 \text{ X } 566} = 1.68$$

The odds that **Poor Health** was because of physical violence was **1.68** as compared to **Good Health**.

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Example: Cross-sectional Study (Cont…)

Example: Women's Health & Life Events

Physical Violence	Depressive Disorder	No Depressive Disorder	Odds Ratio
Yes	81	1020	
No	38	1122	

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Example: Cross-sectional Study (Cont…)

Example: Women's Health & Life Events

Physical Violence	Depressive Disorder	No Depressive Disorder	Odds Ratio
Yes	81	1020	2.34
No	38	1122	1.00

$$OR = \frac{81 \text{ X } 1,122}{1,020 \text{ X } 38} = 2.34$$

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Odds Ratio: Example (Case-control Study)

Example: Endometrial Cancer and Estrogen

Estrogen	Endometrial Cancer Cases	Controls	Odds Ratio
Yes	80	100	
No	120	300	

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Example: Case-control Study (Cont…)

Example: Endometrial Cancer and Estrogen

Estrogen	Endometrial Cancer Cases	Controls	Odds Ratio
Yes	80	100	2.00
No	120	300	1.00

$$OR = \frac{80 \text{ X } 300}{100 \text{ X } 120} = 2.00$$

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Odds Ratio: Example (Case-control Study)

Example: CHD and Smoking

Smoking	Cases	Controls	Odds Ratio
Yes	25	10	
No	75	90	

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Example: Case-control Study (Cont…)

Example: CHD and Smoking

Smoking	Cases	Controls	Odds Ratio
Yes	25	10	3.00
No	75	90	1.00

$$\mathbf{OR} = \frac{\mathbf{25\ X\ 90}}{\mathbf{10\ X\ 75}} = \mathbf{3.00}$$

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When Can the Odds Ratio be Used to Approximate the Relative Risk?

	D+	D-	Total	Risk
E+	a	b	a+b	a/a+b
E-	c	d	c+d	c/c+d

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} \approx \frac{\frac{a}{b}}{\frac{c}{d}} \approx \frac{ad}{bc} = OR$$

For a rare disease, a <<< b, so a+b ≈ b

c <<< d, so c+d ≈ d

Interpretation of the OR

- **OR** can be b/t **0 and ∞**
- **OR =1** indicates **no association** b/t the risk factor and disease status

➢ RR of 1 means the incidence of a diseases among exposed and non exposed is identical.

  ➢ No association

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Interpretation cont'd…

- **RR=/=1, there is an association**
  - **OR <1** indicates **reduced odds** of the disease among subjects
  - **OR >1** indicates **increased odds** of having the disease among subjects **with the risk factor (**an increased risk among exposed than in non-exposed.
    - Positive association

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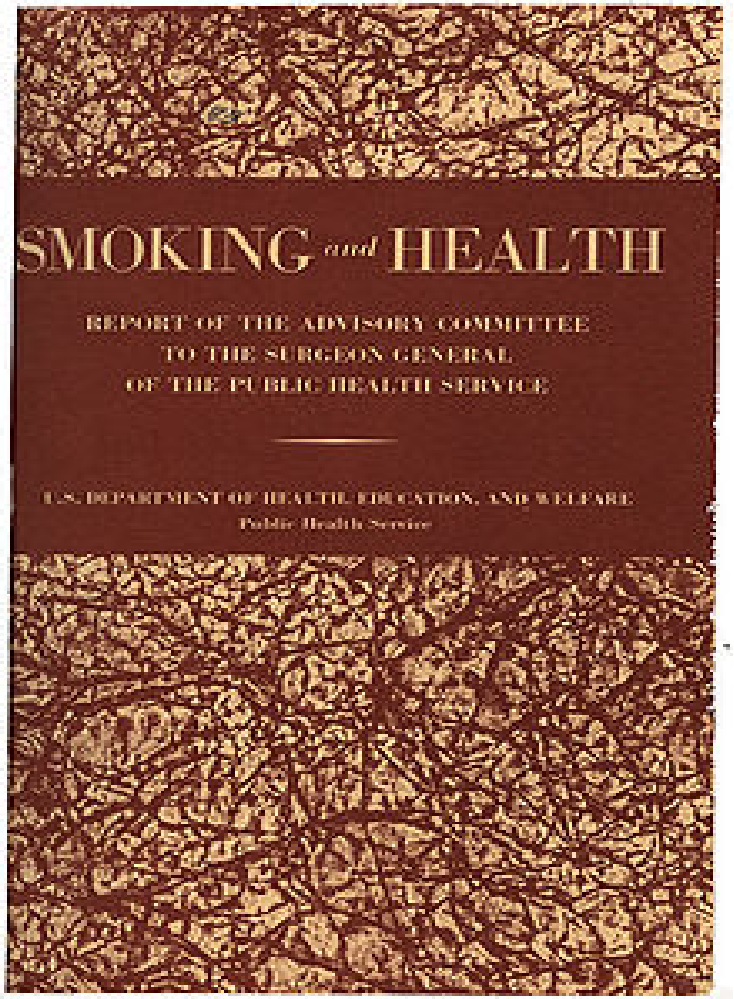
Criteria for the Causal Nature of an Association

- The "Criteria for the causal nature of an association" were first put forth by **Sir Austin Bradford Hill**
- But have been described in various forms since,
  - Each with some modification.
- Probably the best known description of them was in the first **Surgeon General's Report** on
  - **Smoking and Health**, published in 1964.


SMOKING and HEALTH
REPORT OF THE ADVISORY COMMITTEE
TO THE SURGEON GENERAL
OF THE PUBLIC HEALTH SERVICE
U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

https://profiles.nlm.nih.gov/NN/B/B/M/Q/_/nnbbmq.pdf

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Criteria for the causal nature of an association

1. **Coherence** with existing information (also called biological plausibility)
2. **Consistency** of the association
3. **Time sequence**
4. **Specificity** of the association
5. **Strength** of the association
   a. Quantitative strength
   b. Dose–response relationship
   c. Study design

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1. Coherence with existing information or biological plausibility

- Refers to whether the association makes sense,
  - in light of other types of information available in the literature.
- These other types of information could include:
  - data from other **human studies**,
  - data from studies of other **related questions**,
  - data from **animal studies**, or
  - data from **in vitro studies**, as well as
  - **scientific or pathophysiologic theory**.
- **Example:** The association between cigarettes and lung cancer-
  - **cigarette smoke is a known carcinogen**
    - based on **animal data**
    - Cause cancers of the head and neck, the pancreas, and the bladder in **human**

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2. The Consistency of the Association

- Reproducibility of the association in different settings which includes
  - different **geographic settings**,
  - different **study designs**,
  - different **populations**
- For example, in the case of cigarettes and lung cancer, the association has now been reproduced
  - in many different studies,
  - in different geographic locations,
  - using different study designs.

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3. Time sequence

- A cause must precede an effect.
- Although this may seem obvious,
  - there are study designs from which this cannot be determined.
- Example: cigarette smoking usually precedes the lung cancer

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4. Specificity

- Refers effect and whether the effect ever occurs without the presumed cause.
- This criterion is almost **never met in biology**, with the occasional exception of **infectious diseases**.
- It provides **extremely strong support** for a conclusion that an association is **causal if the criteria met**

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5. Strength of the Association

5a. Quantitative Strength of an Association

- Refers to the effect size. To evaluate this,
  - One asks whether the magnitude of the observed difference between the two study groups is large.
- A quantitatively **large association** can only be created by **a causal association or a large error,**
  - which should be apparent in evaluating the methodology of a study.
- A quantitatively **small association** may still be causal,
  - but it could be created by a subtle error, which would not be apparent in evaluating the study.

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5b. Dose–response relationship

– Exists when an increase in the intensity of an exposure results in an increased risk of the disease under study.

– Equivalent to this is a **duration–response relationship**
  - which exists when a longer exposure causes an increased risk of the disease.

– The presence of either a dose–response relationship or a duration–response relationship strongly implies that an association is, in fact, a causal association.

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5c. Study design used

- It refers whether the study was well designed,
  - whether the study was subject to one of the three errors namely
    - random error,
    - bias, and
    - confounding.
- And which study design was used in the studies in question.

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2.5. Types of Epidemiologic Study Designs

- **Pharmacoepidemiology applies** the **methods of epidemiology** to the content area of clinical pharmacology

- Different study designs can be applied within pharmacoepidemiology, all with their own
  - Specific indications,
  - Advantages and
  - Disadvantages

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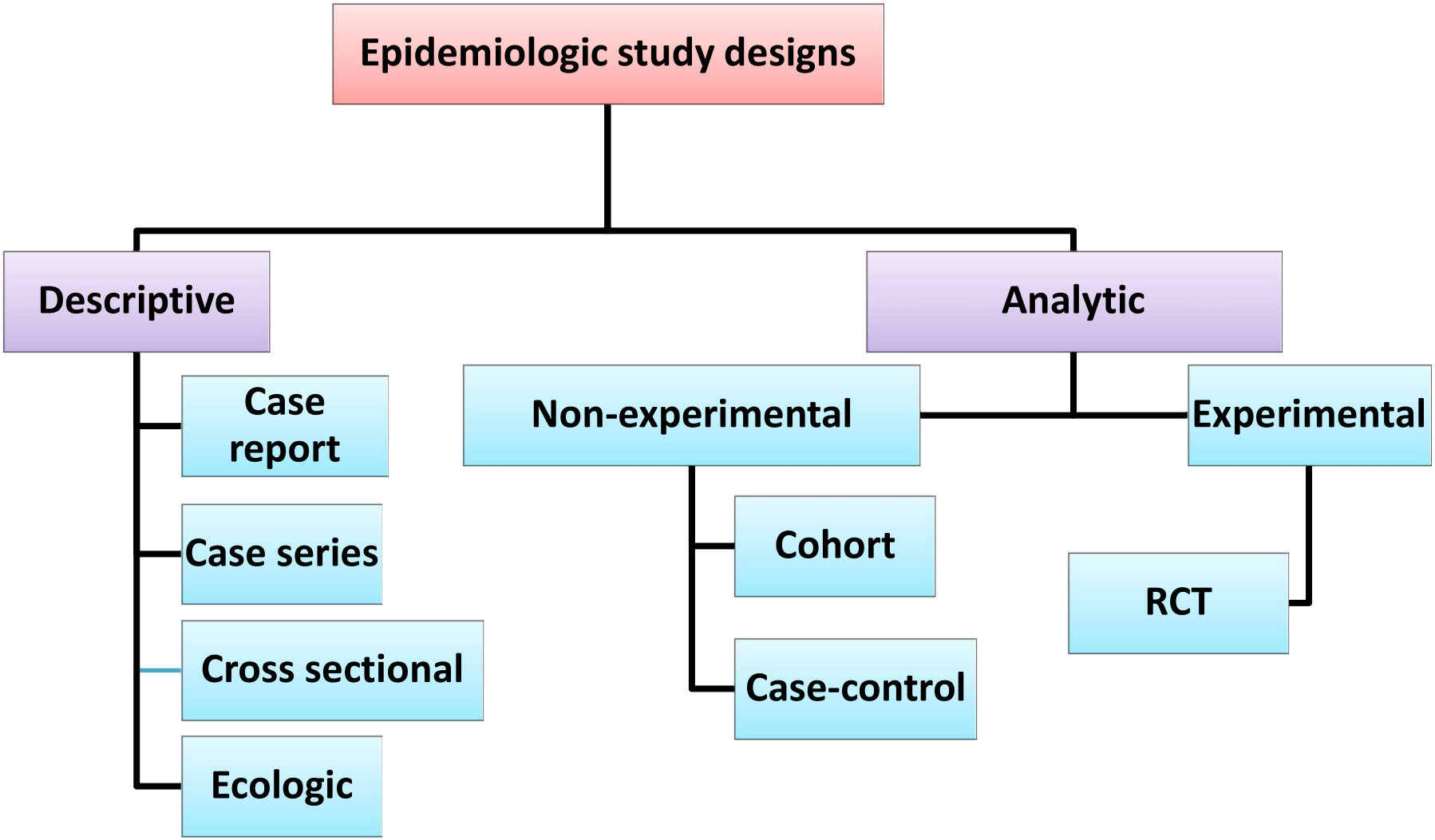

Fig. Types of epidemiologic study designs

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Observational Studies

= Investigator has no control over exposure

- Descriptive
  - Case reports & case series (Clinical)
  - Cross-sectional (Epidemiological)

- Analytical
  - Cohort
  - Case-control
  - Ecological

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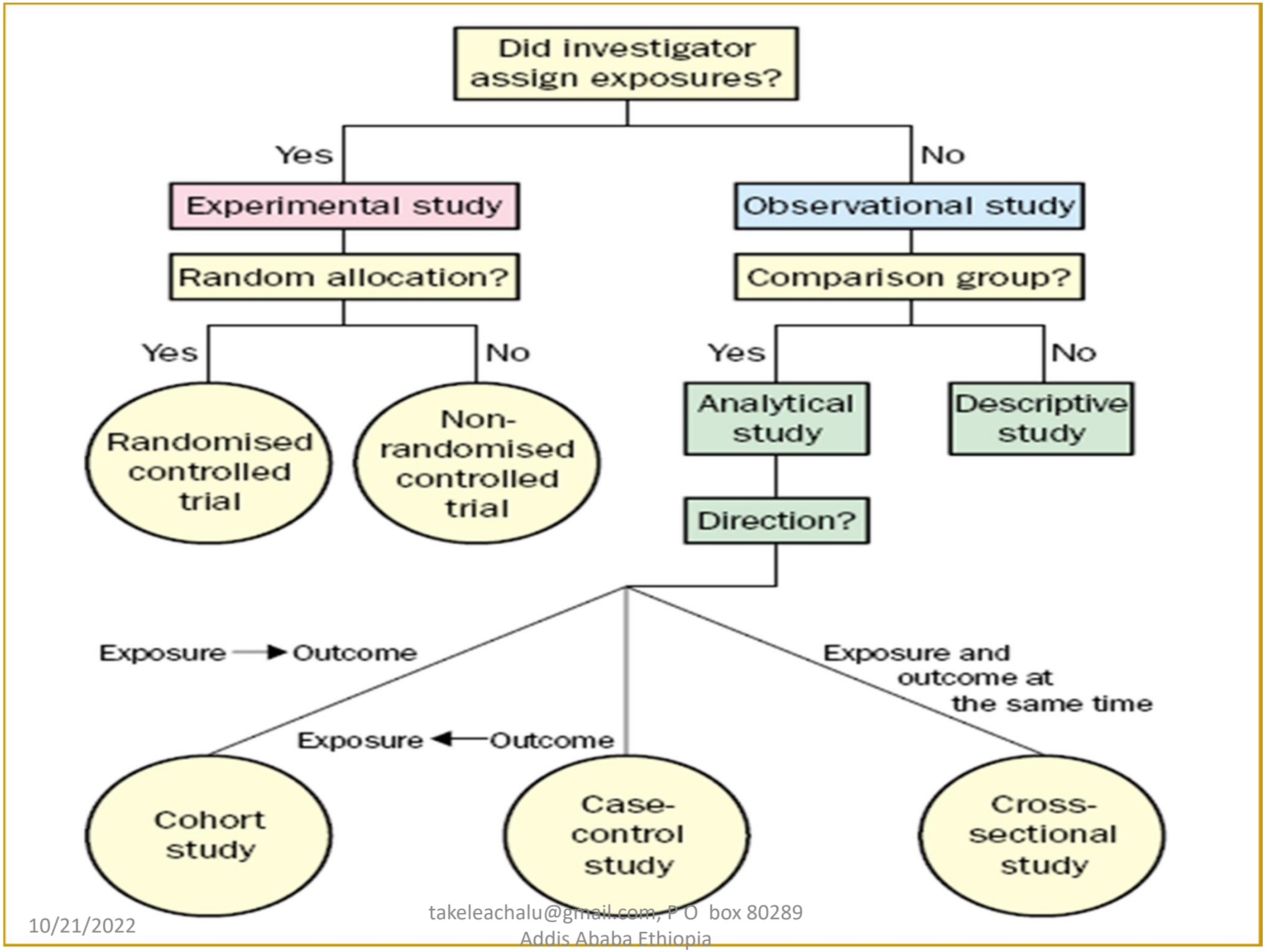

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Hierarchy of Designs and Strength of Evidence

1. Randomized Controlled Trial (RCT)
2. Cohort: Prospective or retrospective)
3. Case control- Prospective or retrospective
4. Cross sectional
5. Case reports/ Case Series
6. Systematic reviews, Meta-analysis: secondary data analysis

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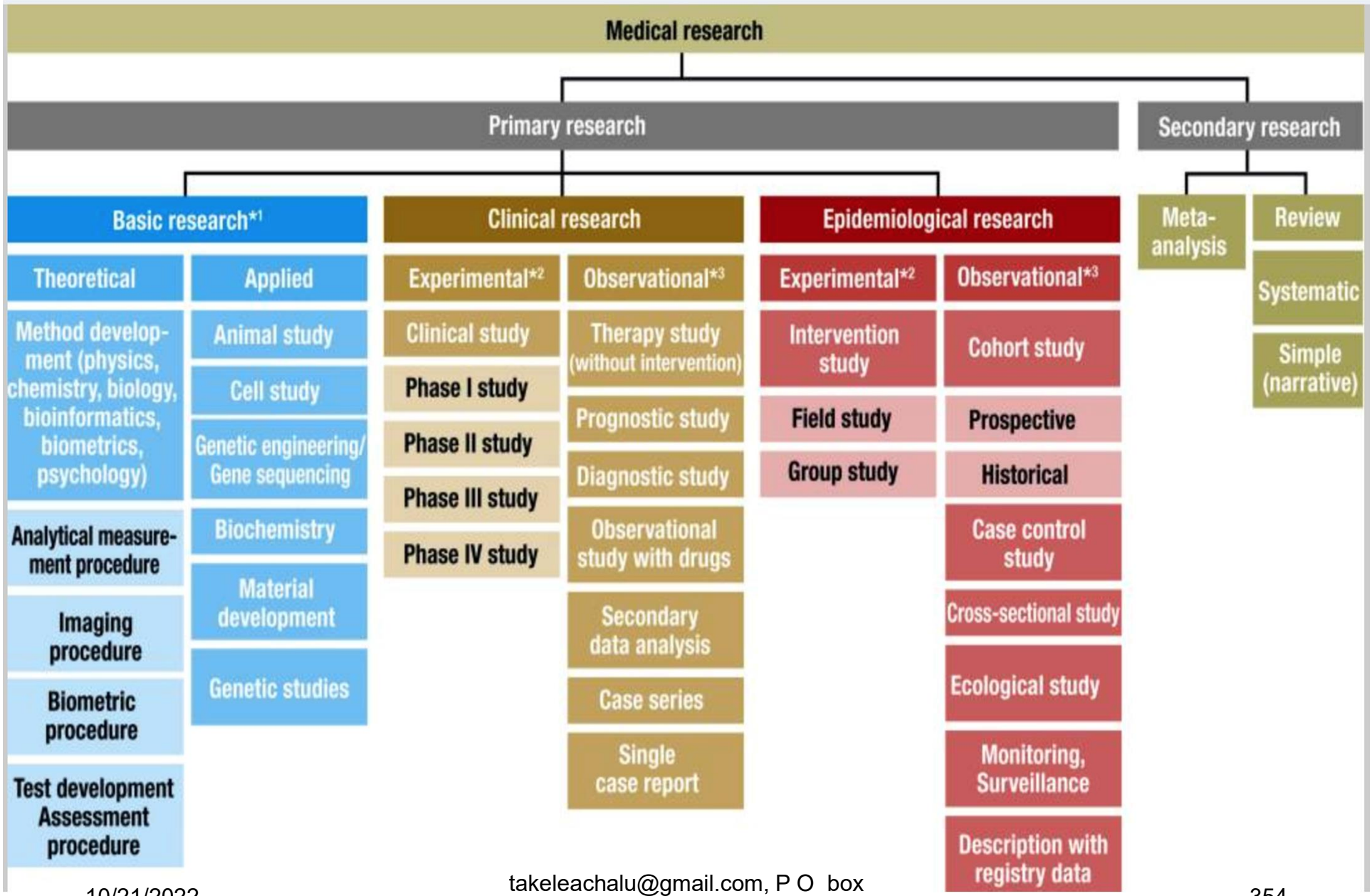
Classification of Medical/ Health sciences research



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Research Design

- The researcher has to make a plan of action before starting the research. The plan of study of a researcher is called the research design.

- It is a comprehensive plan of the series of operations that a researcher intends to carry out to accomplish the research objectives.

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Epidemiological Research

- **Lab research**: applies knowledge of basic sciences towards development of procedures and strategies to prevent, control and understand mechanisms of health-related phenomena
- **Epidemic investigations**: study of outbreaks, in local populations, to identify agent(s), transmission mode(s), and possible control measure(s)
- **Population-based (field) research:** study of distribution, determinants, control measures of health-related phenomena in chosen populations, followed by application of suitable biostatistical techniques which may allow generalization of results

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Study Design

- A study design is the process that guides researchers on how to collect, analyze and interpret observations.
- Study design is the procedure under which a study is carried out.
- It is a l*ogical model* that guides the investigator in the various stages of the research.

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Study design: Definition

A study design is a specific plan or protocol for conducting the study, which allows the investigator to translate the conceptual hypothesis into an operational one.

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Comparison (II)

Qualitative

- **Methods**
  - Focus Groups
  - Interviews
  - Surveys
  - Self-reports
  - Observations
  - Document analysis
  - **Sampling**: Purposive
- **Quality Assurance:**
  - **Trustworthiness**: Credibility, Confirmability, Dependability, Transferability
  - **Authenticity:** Fairness, Ontological, Educative, Tactical, Catalytic

Quantitative

- **Methods**
  - Observational
  - Experimental
  - Mixed
  - **Sampling**: Random (simple, stratified, cluster, etc) or purposive
- **Quality Assurance**:
  - **Reliability:** Internal and External
  - **Validity**: Construct, Content, Face

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Observational Designs (Classification II)

- **Preliminary** (case-reports, case-series)
- **Basic** (cross-sectional, case-control, cohort [prospective, retrospective])
- **Hybrid** (two or more of the above, nested case-control within cohort, etc)
- **Incomplete** (ecological, PMR, etc)
- **Others** (repeated, case cross-over, migrant, twin, etc)

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Case-series:
Clinical case series

- **Clinical case-series:** usually a coherent and consecutive set of cases of a disease (or similar problem) which derive from either the practice of one or more health care professionals or a defined health care setting, e.g. a hospital or family practice.
- A case-series is, effectively, a register of cases.
- Analyse cases together to learn about the disease.
- Clinical case-series are of value in epidemiology for:
  - Studying symptoms and signs
  - Creating case definitions
  - Clinical education, audit and research

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Selection of study design depends on:

- State of knowledge
- Type of information you want to obtain
- The nature of the problem
- The resources available
- Personal experience
- Audience

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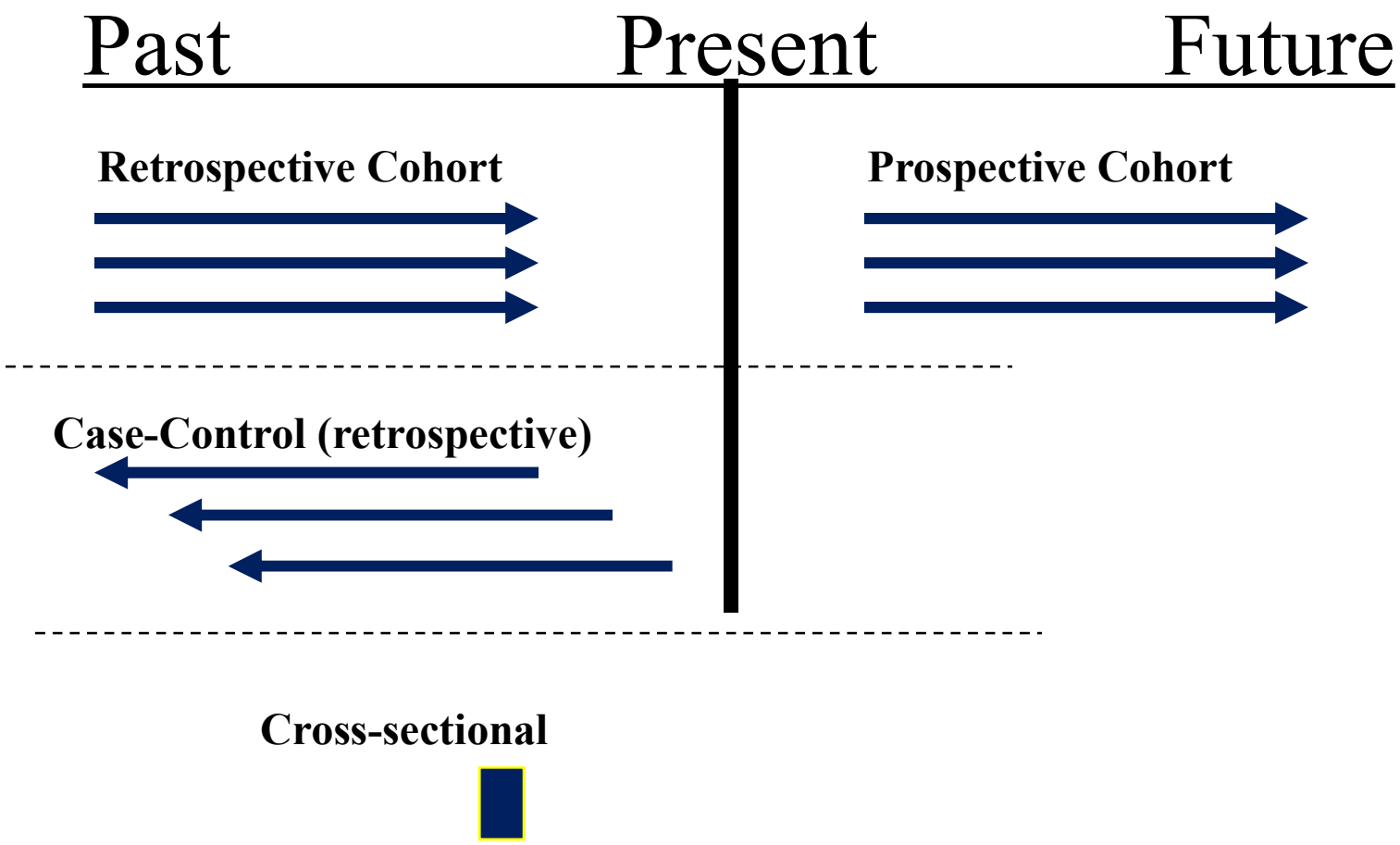
Study design



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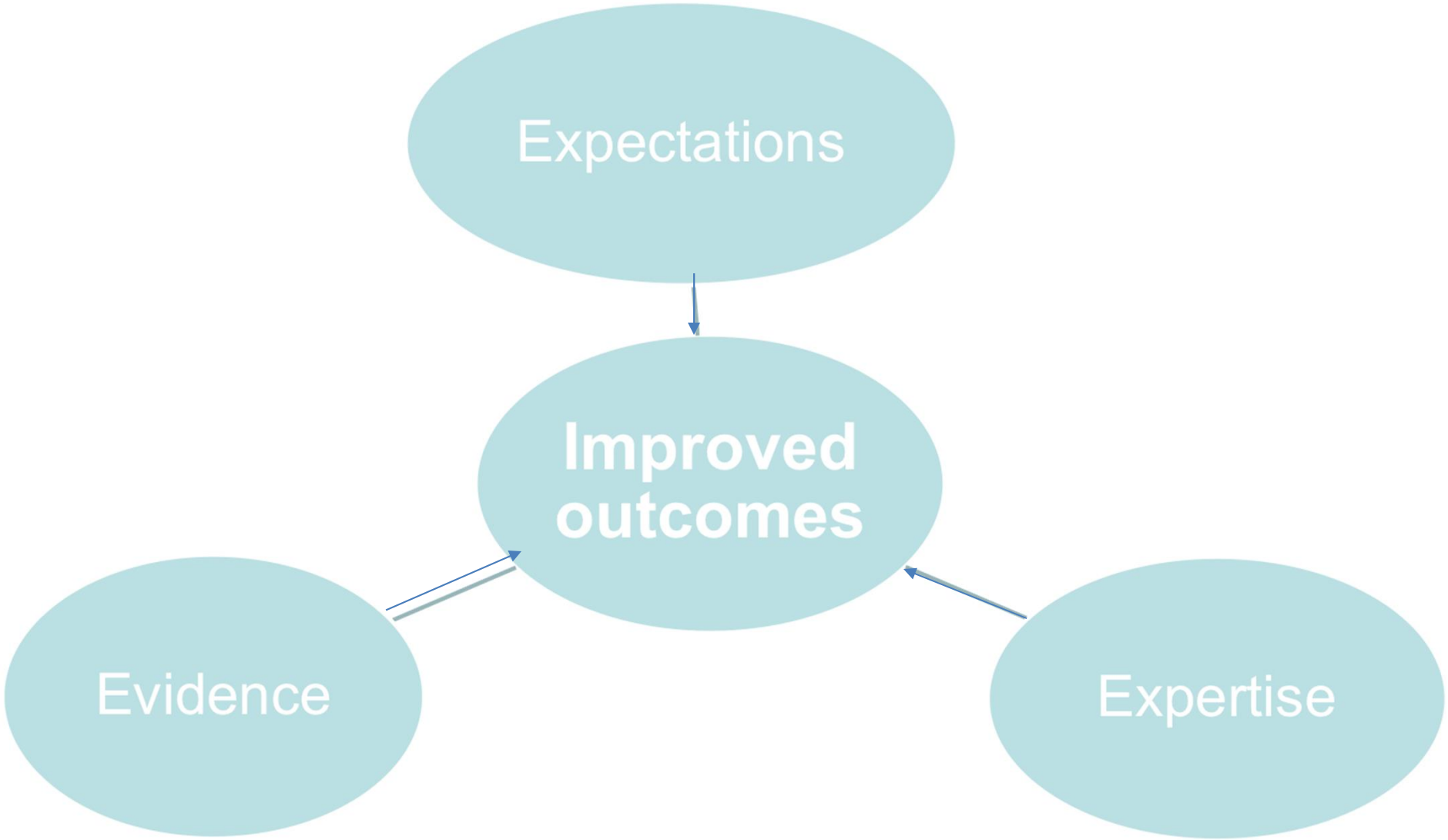

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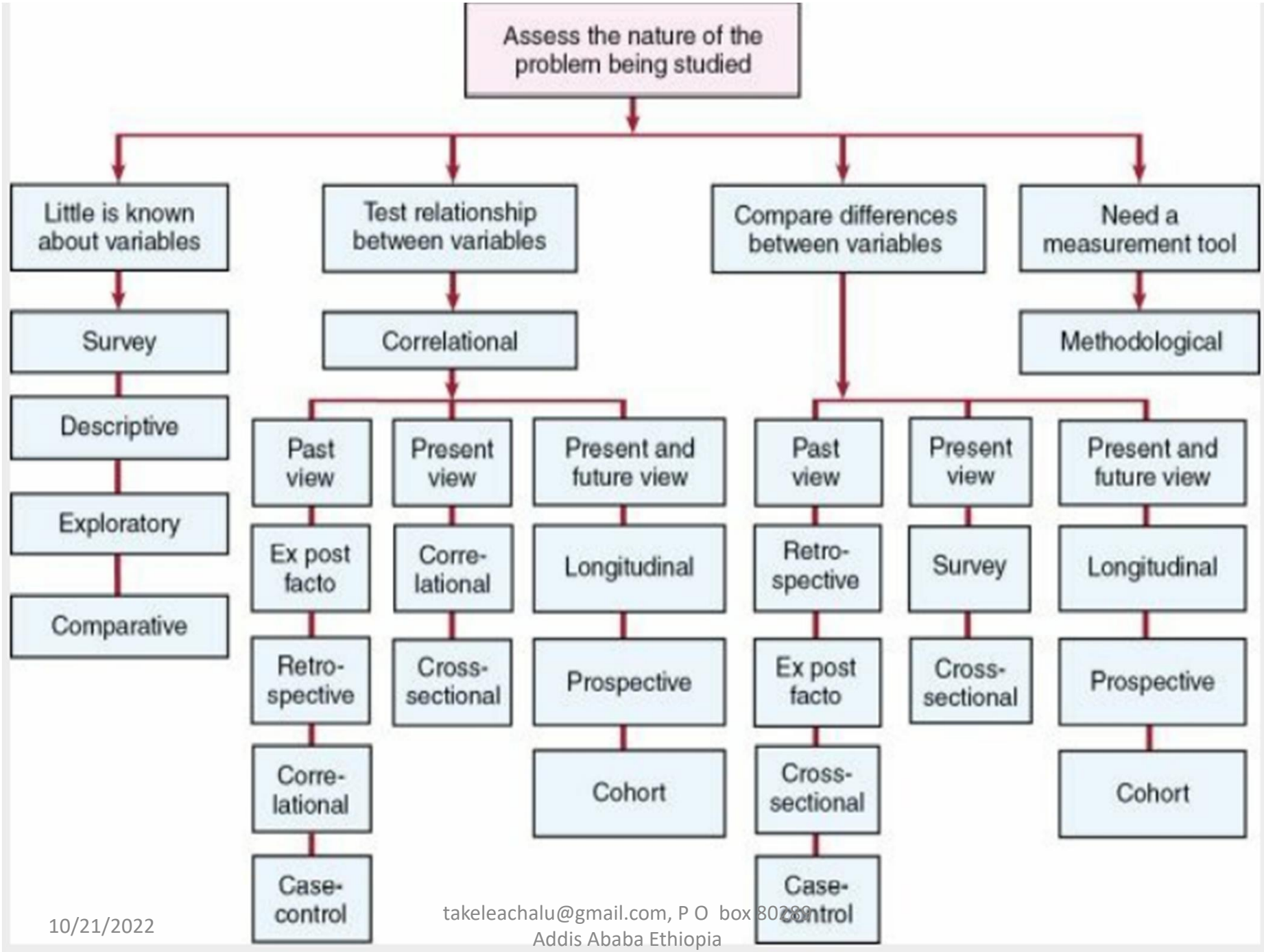

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Conducting Health Sciences …

1. Get started
   - Thinking of an idea
2. Turn the idea in to a research question
3. Review the literature
   - know what is known about your idea
4. Design the study and develop the methods
5. Write your proposal
6. Obtain ethical approval
7. Collect and manage the data
8. Analyze and interpret the data
9. Write a manuscript
10. Disseminate the finding

Environment should be

- Supportive
- Motivating
- Challenging
- Non threatening

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Retrospective and Prospective Designs

- **Retrospective design**
  - the research question or hypothesis is conceived and studied using ***data that were collected and recorded previously*** (before the design of the current study).

- **Prospective, or longitudinal, design**
  - the collection of data is planned in advance and actually occurs after the study has begun.

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Prospective vs. Retrospective (Concurrent vs. Non-concurrent)

- **Prospective cohort-** Healthy cohort (free of the disease) assembled and followed. More reliable than retrospective

- **Retrospective (historical) cohort**- the study is initiated at a point in time after both the exposure and disease have already occurred.
- It is constructed retrospectively through existing records

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Comparison of Retrospective and Prospective Approaches

Retrospective	Prospective
Inexpensive to conduct	Expensive to conduct
Completed in a shorter time period	Completed over a longer time period
Easier to access a larger number of subjects	More difficult to access subjects and usually requires a larger number of subjects
Allows results to be obtained more quickly	Exposure status and diagnostic methods for disease may change
Useful for studying exposures that no longer occur	**Loss of subjects from the study over time may be substantial**
Information and data may be less complete and inaccurate	Information and data may be more complete and accurate
Subjects may not remember past information	Direct access to study subjects enhances reliability of data

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Descriptive studies

- It is a research that describe the characteristics of the population
- Mostly focuses on what questions
- DR includes surveys and fact-finding enquiries of different kinds
- DS is one in which information is collected without changing the environment(i.e., nothing is manipulated).
- Researcher has no control over the variables, only observes and measures the variables.

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Descriptive Studies

- A study in which explain the frequency and relative distributions of health and disease in populations
- Attempt to uncover and portray the occurrence of the condition or problem
- Useful in
  - **Signal detection**,
  - **Hypothesis generating**
  - **Identifying previously unrecognised safety issues**
- Explain **What, Who, Where, When, How much**
  - Person Place Time model

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Descriptive Study Designs

INDIVIDUALS level

- Case reports
- Case series
- Cross sectional surveys

POPULATIONS (GROUPS)

- Ecologic (aggregate) studies

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Analytical Studies

- The aspect of epidemiology concerned with the search for health problem-related causes and effects
- Determine causes or health problems
- Based on Natural exposure
- Use controls or comparison groups
- Focus on the determinants (causes) of diseases
- Ultimate goal is judging whether a particular exposure causes or prevents disease.
  - Test cause–effect relationships

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Case Reports

- A careful, detailed report by one or more clinicians of the ***profile of a single patient.***
- More emphasis is given for unusual findings.
- **Example:** (chaltu satargegne , et.Al (2012). Breast carcinoma in a 7 years old girl. Emj,50:1).
  - It is a rare (<1%) type of breast carcinoma with distinct histologic (tissue related study) features.
- **Strengths-** useful for hypothesis generation.

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Case reports

- Case reports are simply reports of events observed in single patients
- In pharmacoepidemiology,
  - a case report describes a single patient who was exposed to a drug and experiences a particular, usually adverse, outcome.
- Case reports are useful
  - for raising hypotheses about drug effects, to be tested with more rigorous study designs.

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Case series

- **Case series** are collections of patients, all of whom have a **single exposure**, whose clinical outcomes are then evaluated and described.
- Examples
  - Serious liver damage following use of XTC
  - Birth defects after use of Thalidomide (Softenon)

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Ecological Studies (Correlational)

- The study of association between two factors
- Macro level study (can not imply with each individual)
- Studying the trend of health problems
- Examine trends in an exposure that is a presumed cause and trends in a disease that is a presumed effect
  - and test whether the trends coincide.
  - These trends can be examined over time or across geographic boundaries.
- Examples:
  - the association between amount of anti-asthma drug and the increase of asthma mortality among American people
  - **Breast Cancer Incidence by National Fat Intake**

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A cross-sectional study (survey)

- A cross-sectional study examines data at one point in time; that is, data are collected on only one occasion with the same subjects rather than with the same subjects at several time points.

- Cross sectional studies are useful for raising the question of the presence of an association rather than for testing hypothesis with an intervention.

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Cross-sectional Studies

- Prevalence study
- A study design that shows concurrently existing characteristics and health outcomes
- Information about the status of an individual with respect to the presence or absence of exposure and disease is assessed at a point in time.
- Cross sectional studies also show the picture of
  - social,
  - environmental, or
  - other problems or events in a population.
- The point in time may be **as short as few minutes or as long as two or three months.**
  - The time frame of "point in time" is based on the speed of data collection.

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Advantage of Cross-sectional

1. Are a one-step, one-time collection of data
2. are less expensive & more convenient to conduct

3. provide much information useful for planning health services and medical programs
4. In general, measure prevalence rather than incidence

5. Studies are based on a sample of a major population and do not rely on individuals that present themselves for medical treatment.

6. Can study entire populations or a representative sample.
7. Greater generalizability

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Disadvantages of cross sectional studies

1. It is difficult to know which occurred first, the exposure or the outcome. This is known as "chicken or egg dilemma".

2. It may not show strong cause-effect relationships if sample size is small.

3. No time direction between exposure and outcome
4. Susceptible to selection bias (e.g. selective survival)

5. Susceptible to misclassification (e.g. recall)

6. Information on all factors is collected simultaneously, so it can be difficult to establish a putative "cause' antedated the "effect‘.

7. Not good for rare diseases or rare exposures.

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Case-control studies

- Comparing cases with a **disease to controls without the disease**, looking for differences in antecedent exposures.
  - Comparing the diseased and non-diseased groups
  - Look back in time to measure exposures of the study subjects
- Retrospective study
- **Rare diseases**
- Ex. Limb defect and Thalidomide in German babies

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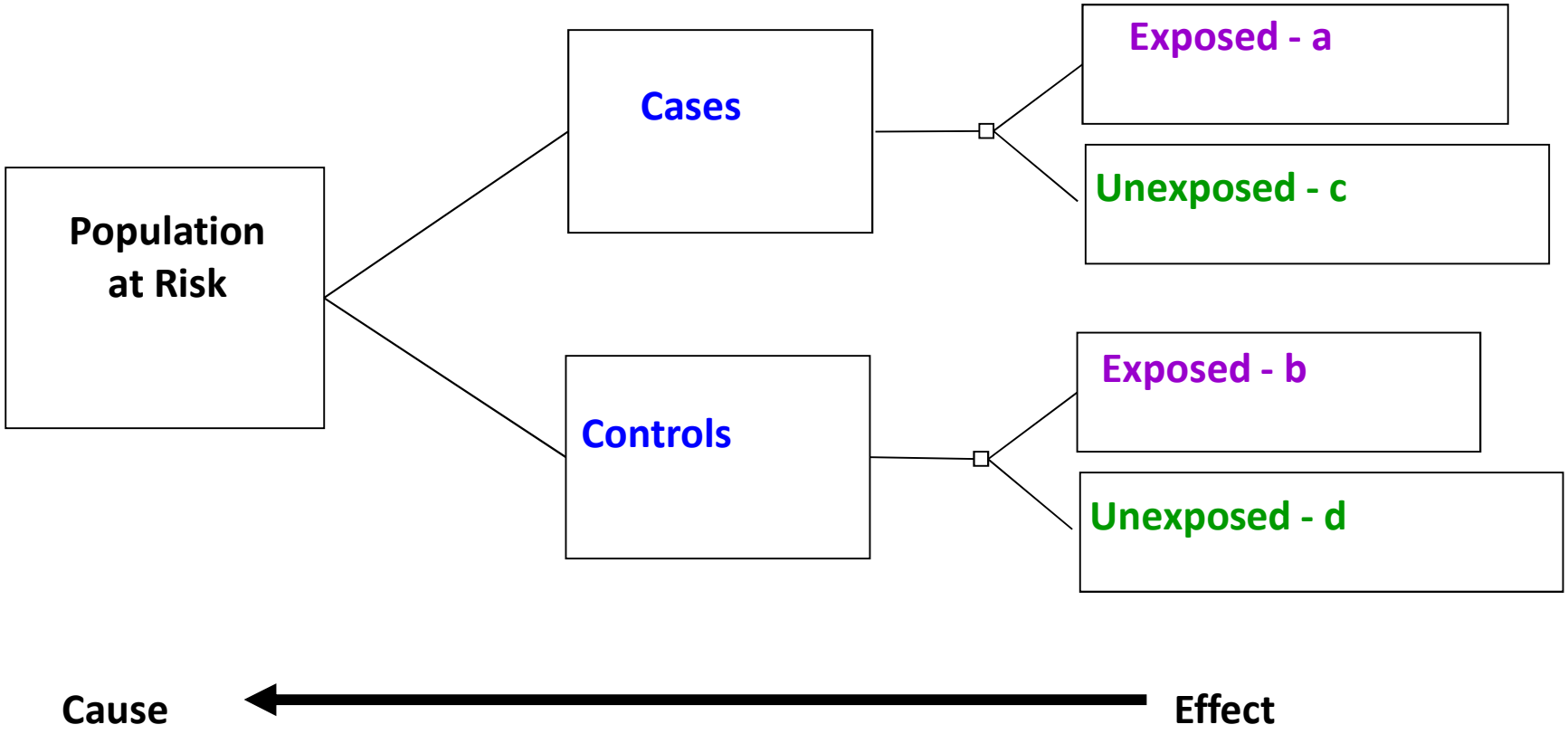
Case-control studies



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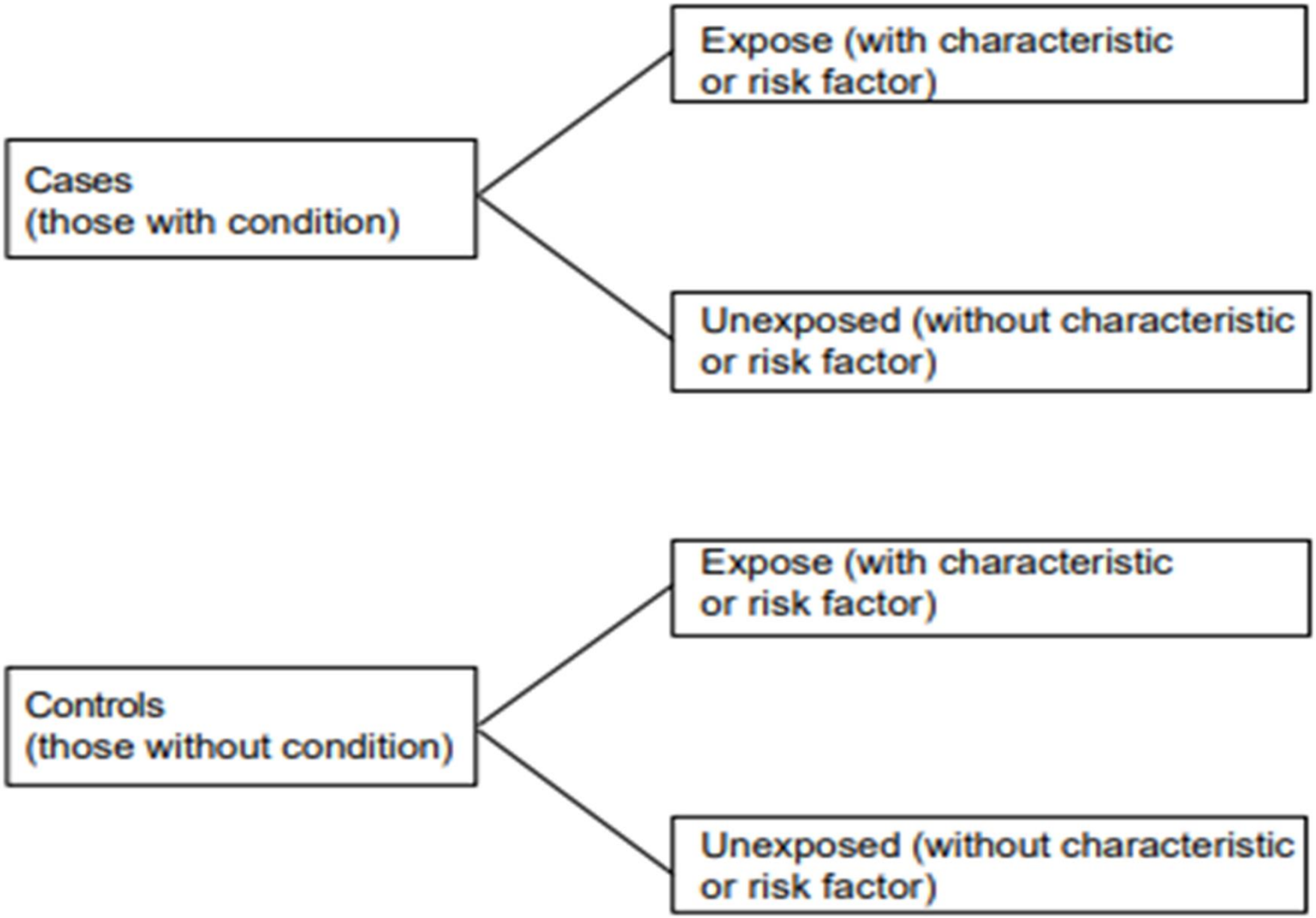
Cases
(those with condition)
Expose (with characteristic or risk factor)
Unexposed (without characteristic or risk factor)
Controls
(those without condition)
Expose (with characteristic or risk factor)
Unexposed (without characteristic or risk factor)

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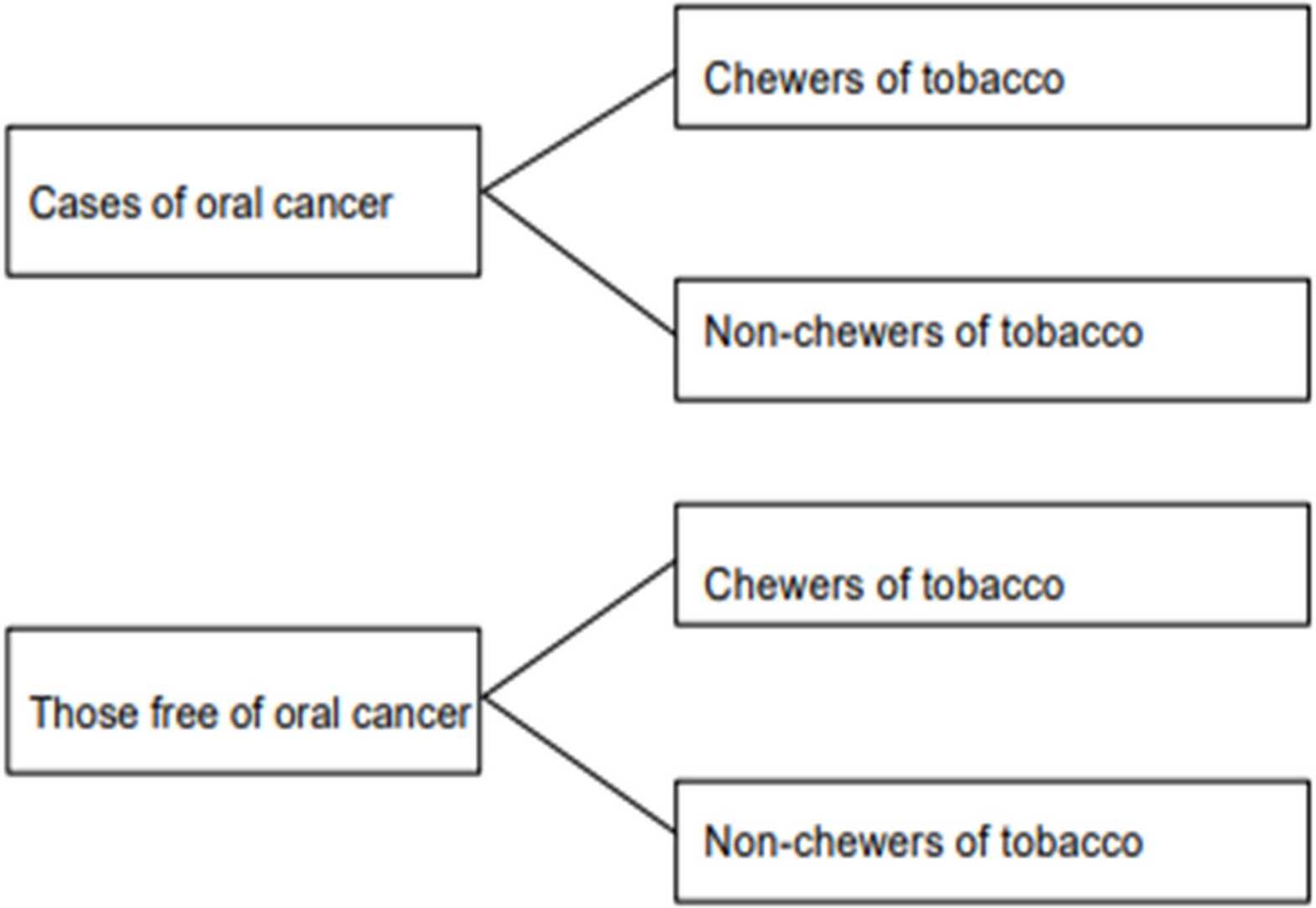
Example



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Steps in conducting case control study

Step 1: Define cases

Step 2: Select cases

Step 3: Select controls

- **The controls should be similar with the cases except that the cases have the disease or other outcome of interest.**

Step 4: Check the exposure status of individuals both in the cases and controls

Step 5: Analysis

- **Prepare 2X2 table**
- **Calculate Odds Ratio (OR)**
- **Perform statistical tests to check whether there is significant association**

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Example case-control study

- What is the risk on breast cancer with the use of **SSRI(**Selective serotonin reuptake inhibitors**) antidepressants**?
- **Cases**:
  - women with breast cancer
- **Controls**:
  - women with no breast cancer
- **Exposure**:
  - SSRIs

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TABLE 2. SSRI* use among cases and controls, New York, New York, Philadelphia, Pennsylvania, and Baltimore, Maryland, 1988–2002†

SSRI use	Cases (no.)	Controls (no.)	OR_1*,‡	95% CI*	OR_2§	95% CI
No use	2,047	2,743	1.0		1.0	
Regular use	59	65	1.5	1.0, 2.1	1.1	0.8, 1.7
<1 year	6	5	2.1	0.6, 7.2	1.6	0.5, 5.4
1–<2 years	21	18	1.9	1.0, 3.6	1.6	0.8, 3.1
2–<4 years	18	20	1.6	0.8, 3.1	1.1	0.6, 2.3
≥4 years	14	22	0.9	0.5, 1.9	0.7	0.4, 1.5
Continuing use	48	50	1.5	1.0, 2.3	1.2	0.8, 1.8
Discontinued use	11	15	1.3	0.6, 3.0	1.1	0.5, 2.6
Sporadic use	19	26	1.1	0.6, 2.1	0.8	0.4, 1.6
Unknown use	1	2				

Coogan et al. Am J Epidemiol 2005

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Calculation OR

		Case	Control
Exposure	+	a	b
	-	c	d
		a + c	b + d

Exposure odds among cases = a/c

Exposure odds among controls = b/d

Exposure Odds ratio (OR) = (a/c) / (b/d)

= (a*d) / (b*c) ≈ RR

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Rofecoxib and risk of MI

Nested Case Control design:

- 9218 MI cases of whom 93 used of rofecoxib < 3 months ago
- 86349 controls, of whom 634 used of rofecoxib < 3 months ago

		MI	control
Rofecoxib	+	93	634
	-	9125	85715

OR (MI)= 93x85715 / 634x9125 = 1.38

BMJ 2005;330:1366

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Selection of cases

- Establish strict diagnostic criteria for the outcome:

  Examples:

  – Type 1 diabetes in children: severe symptoms, very high BG, marked glycosuria, and ketonuria.

  – Type 2 diabetes: few if any symptoms, Slightly elevated BG, diagnosis “complicated”.

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Selection of cases

- Population-based cases: include all subjects or a random sample of all subjects with the disease at a single point or during a given period of time in the defined population:
  - Disease registers

- Hospital-based cases:

  All patients in a hospital department at a given time

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Selection of Controls

Principles of Control Selection:

- Study base:
  - Controls can be used to characterise the distribution of exposure
- Comparable-accuracy
  - Equal reliability in the information obtained from cases and controls → no systematic misclassification
- Overcome confounding
  - Elimination of confounding through control selection→ matching or stratified sampling

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Selection of Controls

- **General population controls:**
  - registries, households, telephone sampling
  - costly and time consuming
  - recall bias
  - eventually high non-response rate
- **Hospitalised controls:**
  - Patients at the same hospital as the cases
  - Easy to identify
  - Less recall bias
  - Higher response rate

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Ascertainment of outcome and exposure status

- **External sources:**
  - Death certificates, disease registries, Hospital and physicians records etc.

- **Internal sources:**
  - Questionnaires and interviews, information from a surrogate (spouses or mother of children), biological sampling(e.g. antibody)

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Strengths and Limitations of Case-Control

Strengths

- Quick, inexpensive
- Well-suited to the evaluation of diseases with long latency period
- Rare diseases
- Examine multiple etiologic factors for a single disease

Limitations

- Not rare exposure
- Incidence rates cannot be estimated unless the study is population based
- Selection Bias and recall bias

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Cohort Studies

- Are studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome.
- Cohort studies generally are used to compare exposed patients to unexposed patients
  - Although they can also be used to compare one exposure to another.
- The design best allows for estimates of the probability or risk of developing the outcome
- The exposed or not exposed to a particular risk factors
- Measuring incidence
- **The best design of observational studies that can explain causation of health problems**

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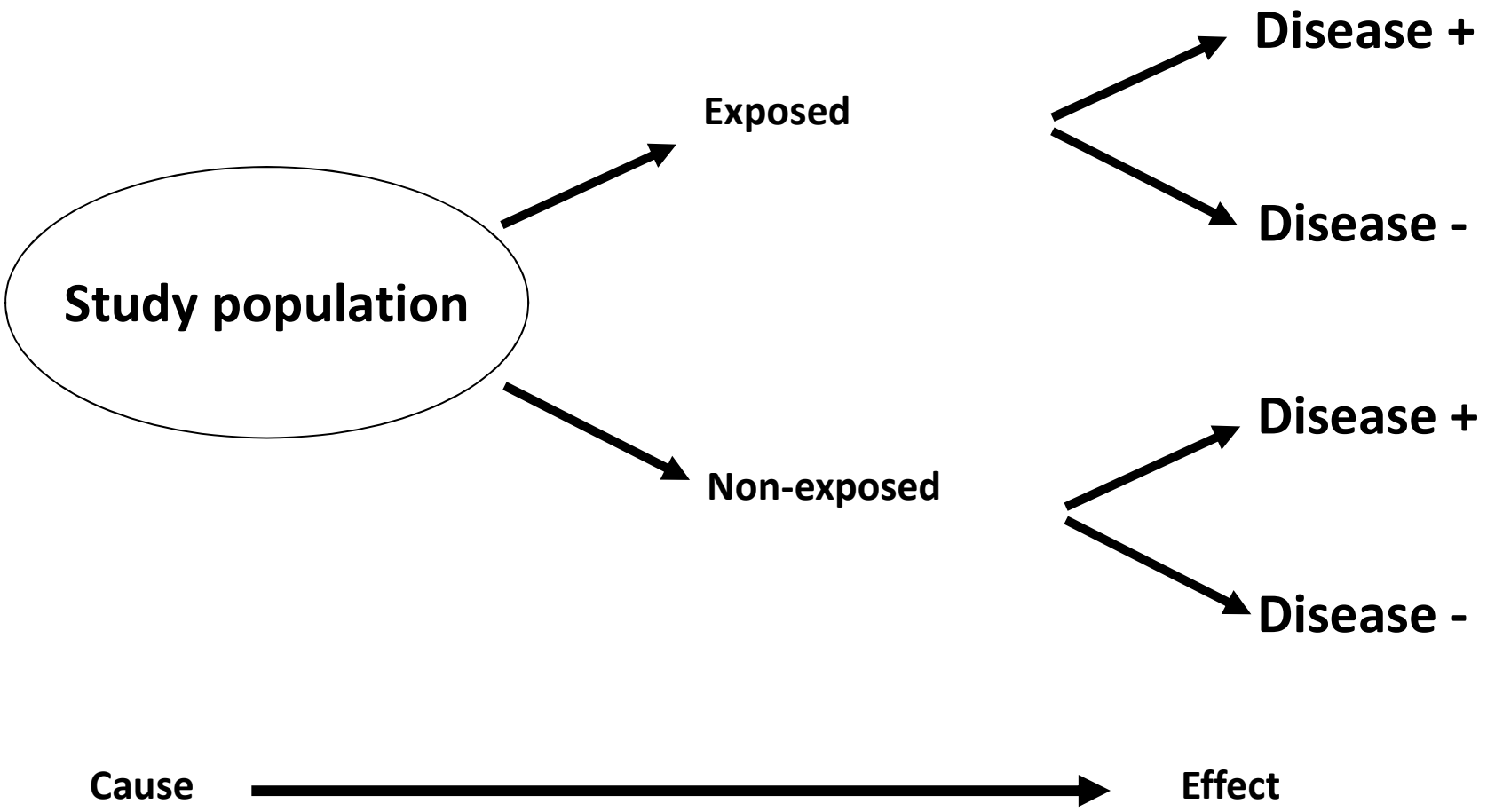
Cohort study / Follow-up study



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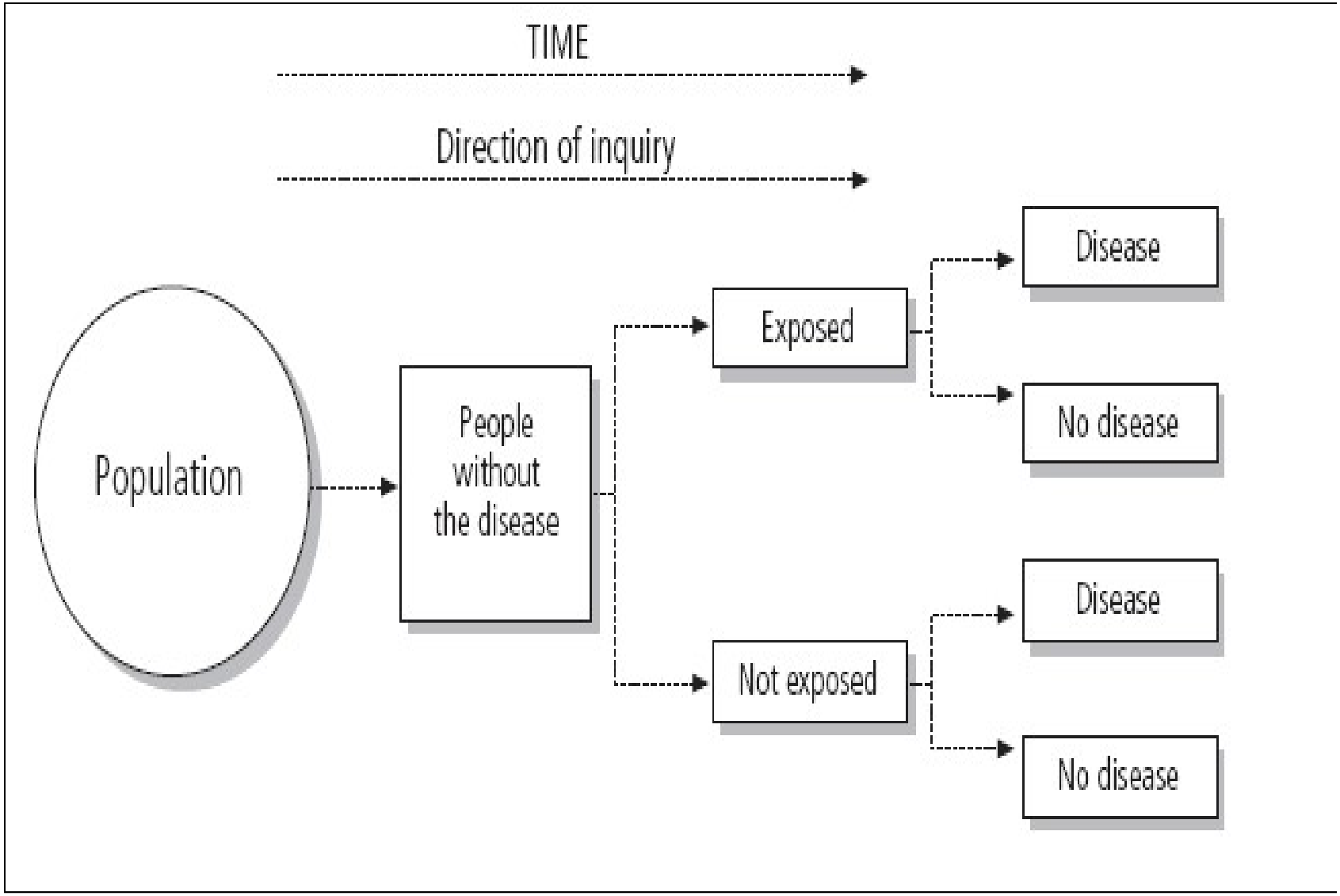

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Strengths and Limitations of Cohort Study

Strength

- **Rare exposure**
- Examine multiple effects of a single exposure
- **Minimizes bias** in the exposure determination
- Direct measurements of incidence of the disease

Limitation

- **Not rare diseases**
- **Prospective**: Expensive and time consuming
- **Retrospective**: in adequate records
- Validity can be affected by losses to follow-up

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Steps in conducting cohort study

Step 1: Define exposure

Step 2: Select exposed group

Step 3: Select non-exposed group

Step 4: Identify sources of data for exposure and outcome

Step 5: Collect data

Step 6: Analyze data

- Prepare 2X2 table
- Calculate Relative Risk (RR)
- Perform statistical tests to check whether there is statistical significant association

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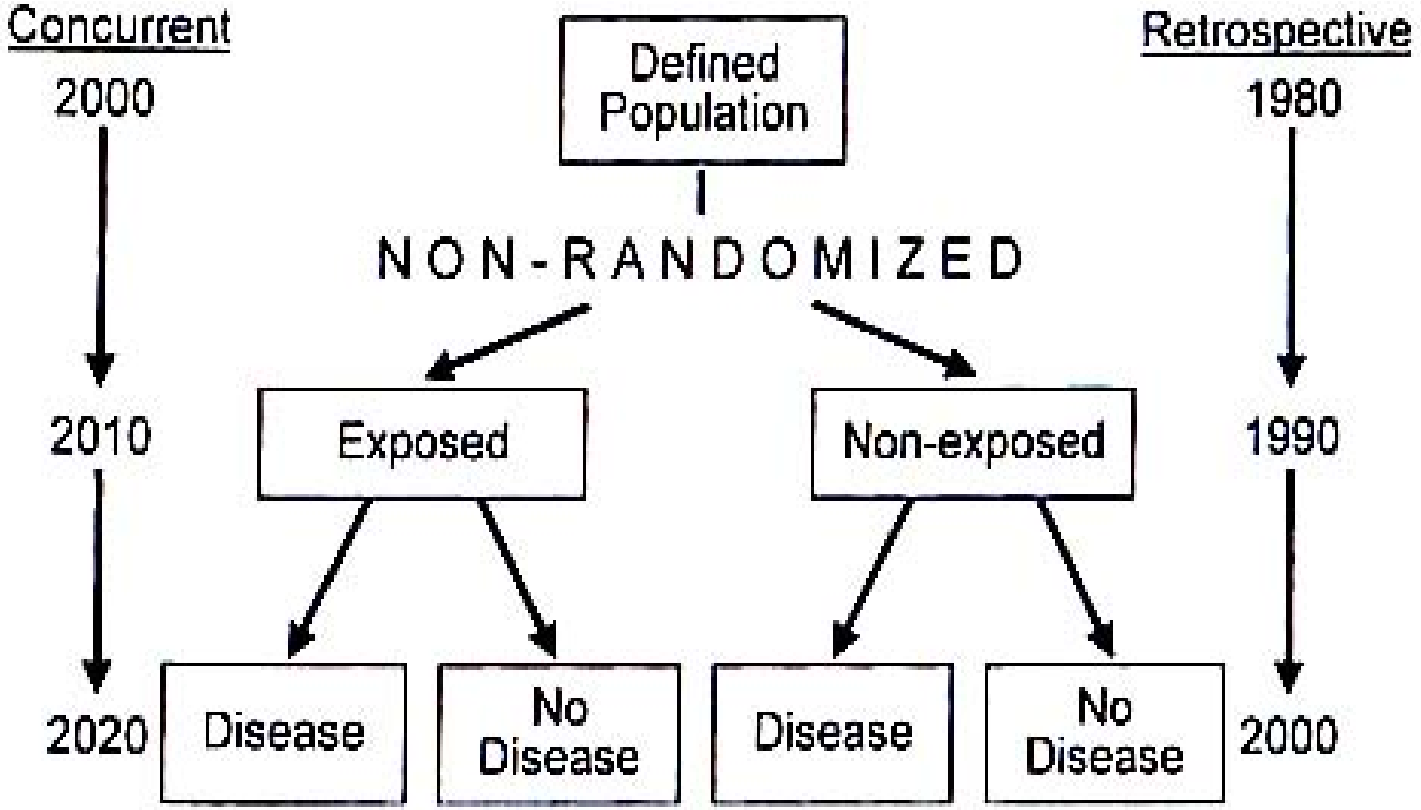
Concurrent VS Retrospective Cohort

Prospective or



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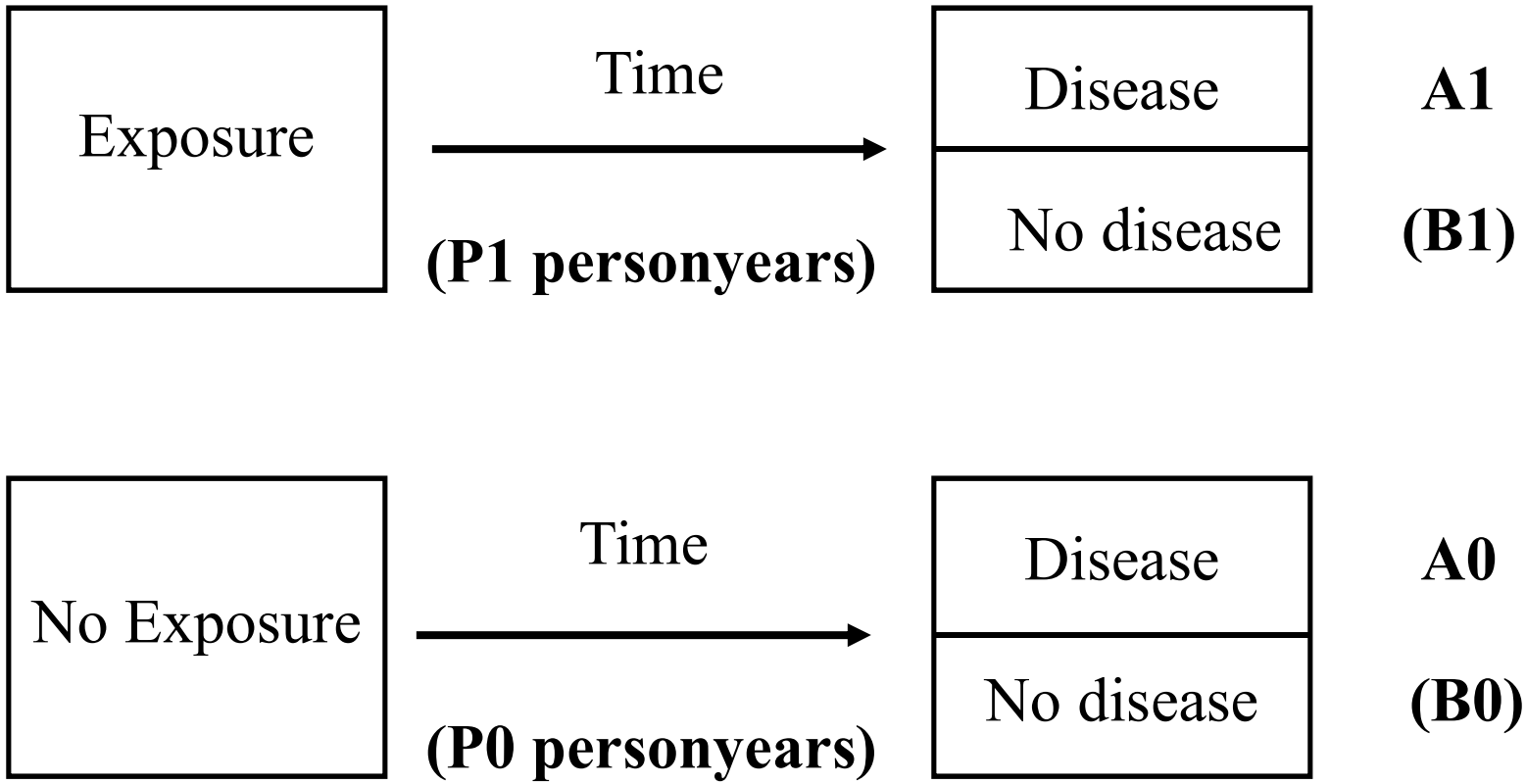
Frequency measures cohort study



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Frequency measures

- Incidence
  - Cumulative incidence (CI)
  - Incidence rate (IR)

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Frequency measures cohort study

		Disease	No disease	Total
Exposure	+	A1	B1	N1
	-	A0	B0	N0

Risk disease + | exposure + = A1 / N1 = CI_1

Risk disease + | exposure - = A0 / N0 = CI_0

Frequency measures cohort study

		Disease	Person-years
Exposure	+	A1	P1
	-	A0	P0

Force of morbidity | exposure + = A1 / P1 = IC_1

Force of morbidity | exposure - = A0 / P0 = IC_0

Effect measures cohort study

Risk difference	**RD**	**$CI_1 - CI_0$**	**$IC_1 - IC_0$**
Relative Risk	RR	CI_1 / CI_0	IC_1 / IC_0
Attributable Risk	AR	$(CI_1 - CI_0) / CI_1$	$(IC_1 - IC_0) / IC_1$
Relative Risk Reduction	RRR	1 – RR	
Number needed to treat	NNT	1 / RD	

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Pill and Deep Venous Thrombosis

Risk no pill = 3.9 per 100 000 py

Risk pill gen. 2 = 10.3 per 100 000 py

Risk pill gen. 3 = 21.3 per 100 000 py

$RR_{2/3}$ = 2.07

$RV_{2/3}$ = 11.0 per 100 000 py

$AR_{2/3}$ = 52%

‘NNH’$_{2/3}$ = 9091 per year

Lancet 1995; 346: 1582 - 1588

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Prospective vs. retrospective Cohort Studies

- Prospective Cohort Studies
  - Time consuming, expensive
  - More valid information on exposure
  - Measurements on potential confounders
- Retrospective Cohort Studies
  - Quick, cheap
  - Appropriate to examine outcome with long latency periods
  - Admission to exposure data
  - Difficult to obtain information of exposure
  - Risk of confounding

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Selection of the Exposed Population

- Sample of the general population:
  - Geographically area, special age groups, birth cohorts (Framingham Study)
- A group that is easy to identify:
  - Nurses health study
- Special population (often occupational epidemiology):
  - Rare and special exposure
  - Permits the evaluation of rare outcomes

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Selection of the Comparison Population

- **Internal Control Group**
  - Exposed and non-exposed in the same study population (Framingham study, Nurses health study)
    - Minimise the differences between exposed and non-exposed
- **External Control Group**
  - Chosen in another group, another cohort (Occupational epidemiology: Asbestosis vs. cotton workers)
- **The General Population**

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Applications of different observational designs

Application	Ecological	X-sectional	Cohort	Case-control
Rare disease	++++	-	-	+++++
Rare exposure	++	-	+++++	-
Test multiple effects	+	++	+++++	-
Study multiple exposures	++	++	+++	++++
Time relationship	++	-	+++++	+
Direct measure of incidence	-	-	+++++	+

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Bias, Cost, and Time

	Ecological	X-sectional	Cohort	Case-control
Probability of;				
Selection bias	-	medium	low	high
Recall bias	-	high	low	high
Loss of follow up	-	-	high	low
Confounding	high	medium	low	medium
Time required	low	medium	high	medium
Cost	low	medium	high	medium

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Experimental/ Intervention studies

- Longitudinal in design
- There is random allocation of subjects to either group
  - treatment & control group
- Individuals are allocated by the investigator
  - artificial manipulation of study factors
- Can produce high quality data

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- Classification based on the population studied

  1. Clinical trial
     - Usually performed in clinical settings and the subjects are patients
  2. Field trial
     - Used in testing medicine for preventive purpose
     - Subjects are healthy people e.g. vaccine trial
  3. Community trial
     - Unit of the study is group of people/community e.g. fluoridation of water to prevent dental caries

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- Classification based on objective

1. Phase I
   - Trial on small subjects to test a new drug with small dosage to determine the toxic effect
2. Phase II
   - Trial on small group to determine the therapeutic effect
3. Phase III
   - study on large population
   - usually randomized controlled trial

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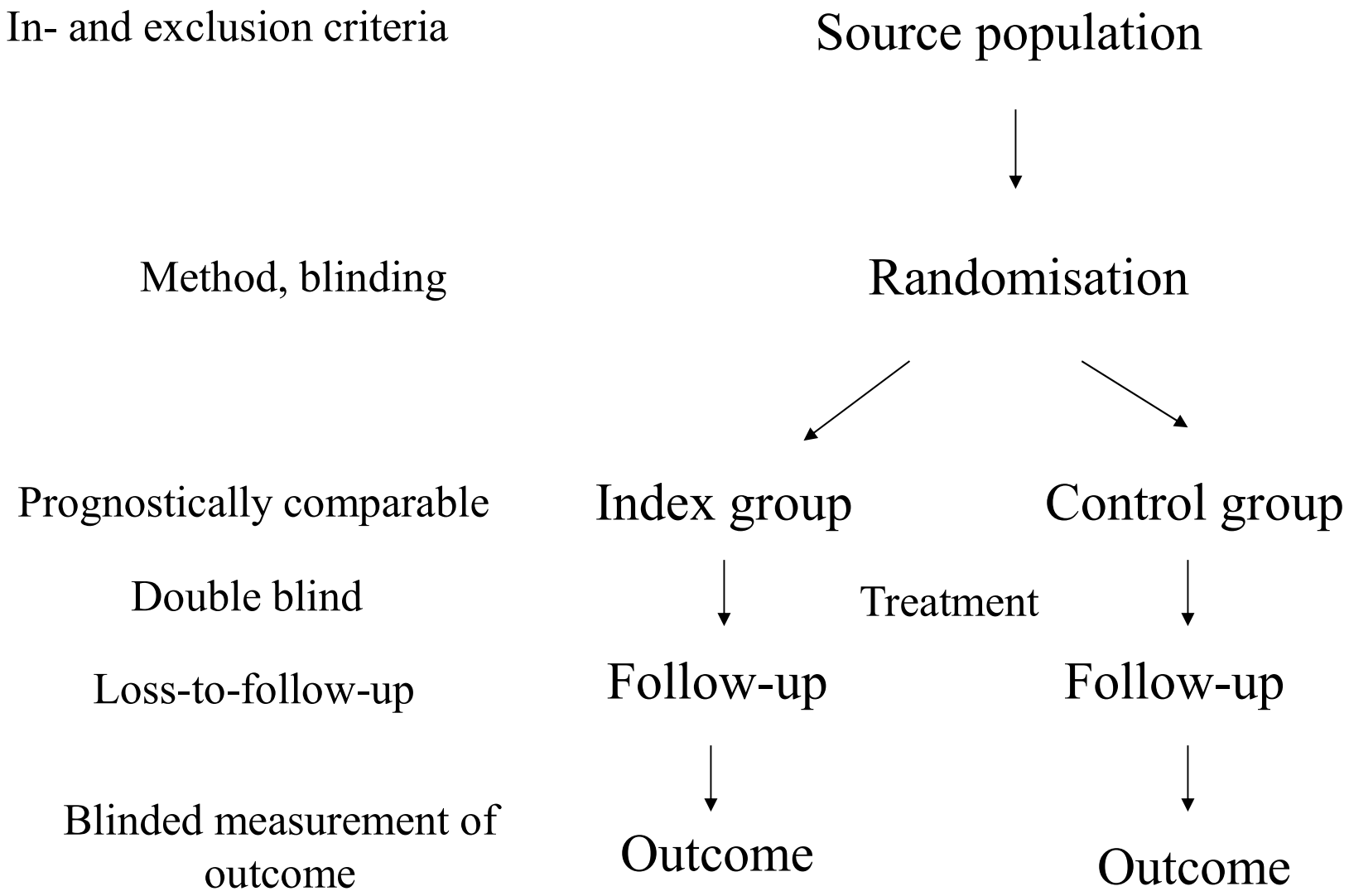

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- In a clinical trial,
  - the experimental group receives the drug or treatment to be evaluated,
  - while the control group receives a placebo, no treatment, or the standard of care.
  - Both groups are followed for the outcome(s) of interest.
- Hawthorne effect : Even “inert” treatments might result in significant improvements in the patient’s condition

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Crossover design

- A crossover study is a special design of controlled intervention study that is sometimes used in drug trials.
- In this design,
  - half of the participants are randomly assigned to start with the placebo and then switch to active treatment, while the other half does the opposite.

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Advantages and Disadvantages of Crossover Study design (RCT)

Advantages:

- It **reduces the number of subjects required**, since each subject serves as both an experimental subject and a control
- It decreases the **biological variability** inherent in comparing different subjects by comparing each subject with himself or herself

Disadvantages:

- Increases the duration of the study
- Carry-over effect
- Fatigue

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Quasi-experimental designs

- Artificial manipulation of the study factor without randomization (e.g. program evaluation)
- One group (internal) comparison
  - Each experimental unit serves as its own control
  - The control will be past experience historical (before and after study)
- Multiple group (external) comparison
  - Treatment or intervention group compared to control or comparison groups

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Designs with Historic control

- A before and after study is a method of control in which results from experimental subjects are compared with outcomes from patients treated before the new intervention was available.
- These are called historic controls.

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Advantages and limitation of RCT (Experimental studies)

- Advantages
  - Gold standard for therapeutic evaluation
  - The Gold standard is achieved through
    - Randomization
    - blindness
    - Use of placebo
- Limitations
  - Ethical considerations (e.g. smoking, birth defects)
  - Feasibility / practical issues (e.g. rare adverse effects)
  - Cost

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Table: Advantages and disadvantages of epidemiologic study designs

Table 2.4. Advantages and disadvantages of epidemiologic study designs

Study Design	Advantages	Disadvantages
Randomized clinical trial (Experimental study)	Most convincing design Only design which controls for unknown or unmeasurable confounders	Most expensive Artificial Logistically most difficult Ethical objections
Cohort study	Can study multiple outcomes Can study uncommon exposures Selection bias less likely Unbiased exposure data Incidence data available	Possibly biased outcome data More expensive If done prospectively, may take years to complete
Case–control study	Can study multiple exposures Can study uncommon diseases Logistically easier and faster Less expensive	Control selection problematic Possibly biased exposure data
Analyses of secular trends	Can provide rapid answers	No control of confounding
Case series	Easy quantitation of incidence	No control group, so cannot be used for hypothesis testing
Case reports	Cheap and easy method for generating hypotheses	Cannot be used for hypothesis testing

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3. Basic principles of clinical pharmacology relevant to pharmacoepidemiology

Clinical pharmacology

- Clinical pharmacology comprises all aspects of the scientific study of medicinal drugs in humans.
- It can be divided into two
  - **pharmacokinetics-** the relationship between the **dose of a drug administered and the serum or blood level achieved**
  - **Pharmacodynamics-** the study of the relationship between **drug level and effect.**
- Its overall objective is
  - to provide the knowledge base needed to ensure rational drug therapy.
- In addition to studying biologic effects of drugs,
  - clinical pharmacology includes the study of
    - non-pharmacologic (e.g., economic and social) determinants
    - and effects of medication use.

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Pharmacotherapeutics

- Pharmacotherapeutics- refers the application of the principles of clinical pharmacology to
  - rational prescribing,
  - the conduct of clinical trials, and
  - the assessment of outcomes during real-life clinical practice.
- Clinical pharmacology tries to explain the response to drugs in individuals
- while **pharmacoepidemiology** is concerned with measuring and explaining variability in outcome of drug treatment in populations.
  - The application of epidemiologic methods to the subject matter of clinical pharmacology.

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- In epidemiologic studies of **non-drug exposures**, it is frequently assumed that
  - the **amount** and **duration** of exposure is **proportional to the risk of the outcome**
- But this proportionality assumptions might not always work in pharmacoepidemiology because of
  - **"depletion of susceptible"-** case which often occur in the first few weeks of treatment, the risk declining thereafter
  - **Exposure to a drug** is never **a completely random** event
    - » There may be confounding factors

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- Because of the high probability of confounding beyond that which can be controlled for using measured variables (i.e., residual confounding),
  - Pharmacoepidemiologists tend to be cautious about the interpretation of weak associations between drug exposure and outcomes.
- When interpreting pharmacoepidemiology studies,
  - it is important to realize that relationships exist between drug response and various biologic and sociologic factors, and to attempt to explore the reasons for them.
  - The discipline of clinical pharmacology has provided us with explanations for some of these variations in response to
    - important drugs, and knowledge of these is necessary when conducting or interpreting pharmacoepidemiology studies

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- The central concepts of clinical pharmacology that are important in pharmacoepidemiology includes
  - Nature of drugs
  - Mechanisms of drug action,
  - Concept of drug potency,
  - Role of pharmacodynamics and pharmacokinetics (including genetic factors that influence these functions), and
  - Importance of human behavior in explaining variability in drug effects.

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- There are many factors that affect an individual's response to a drug.
- These factors include
  - Sex
  - Age
  - Health conditions
  - Concomitant medications, and
  - Genetic makeup.
- Factors that influence individual drug response may do so via
  - Pharmacokinetic mechanisms,
  - Pharmacodynamics mechanisms, or
  - Both
- An important goal of pharmacoepidemiology is
  - to use population research methods to characterize factors that influence individual drug response.

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3.3. Sample Size Calculations for Cohort Studies

- The sample size required for a cohort study depends on what you are expecting from the study.
- To calculate sample sizes for a cohort study, one needs to specify five variables

1. **Type I error (α)**
   - considered tolerable, and
   - whether it is **one-tailed or two-tailed**
2. **Type II error (β)** considered tolerable
3. **Minimum relative risk** to be detected
4. **Incidence of the disease in the unexposed control group**
5. **Ratio of unexposed controls to exposed study subjects**

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Type I error

- That one is willing to tolerate in the study
- Probability of concluding
  - there is a **difference between the groups** being compared
  - when **in fact a difference does not exist**.
- Using diagnostic tests as an analogy
  - A type I error is a **false positive** study finding

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Type II error

- That one is willing to tolerate in the study.
- A type II error is the probability of concluding
  - There is **no difference between the groups** being compared
  - When **in fact a difference does exist**.
- A type II error is the **probability of missing a real difference**
- Using diagnostic tests as an analogy,
  - A **type II error is a false negative study finding**.
- The complement of β **is the power of a study**
  - The probability of detecting a difference if a difference really exists.
  - Power is calculated as $(1-\beta)$.

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- **The minimum effect size** one wants to be able to detect.
  - For a cohort study, this is expressed as a **relative risk**.
- **The expected incidence** of the outcome of interest in the **unexposed control group.**
- **The number of unexposed control subjects** to be included in the study for each exposed study subject.
  - A study has the most statistical power for a given number of study subjects
    - if it has the same number of controls as exposed subjects.
    - However, sometimes the number of exposed subjects is limited and,
    - therefore, inadequate to provide sufficient power to detect a relative risk of interest.
  - In that case, additional power can be **gained by increasing the number of controls alone.**
    - Doubling the number of controls,
      - that is including two controls for each exposed subject, results in a modest increase in the statistical power, but it does not double it.
    - Including three controls for each exposed subject increases the power further.

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Example: Sample Size Formula For Cohort Study

$$N = \frac{1}{[p(1-R)]^2}\left[Z_{1-\alpha}\sqrt{\left(1+\frac{1}{K}\right)U(1-U)} + Z_{1-\beta}\sqrt{pR(1-Rp)+\frac{p(1-p)}{K}}\right]^2$$

$$U = \frac{K_p + pR}{K+1}$$

where

- p is the incidence of the disease in the unexposed,
- R is the minimum relative risk to be detected,
- α is the type I error rate which is acceptable,
- β is the type II error rate which is acceptable,
- $Z_{1-\alpha}$ and $Z_{1-\beta}$ refer to the unit normal deviates corresponding to α and β ,
- K is the ratio of number of control subjects to the number of exposed subjects, and
- $Z_{1-\alpha}$ is replaced by $Z_{1-\alpha/2}$ if one is planning to analyze the study using a two-tailed

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4.4. Sample Size Calculations for Case-Control Studies

- The approach to calculating sample sizes for case–control studies is similar to the approach for cohort studies.
- There are five variables that need to be specified
  1. **Type I error (α)** considered tolerable, and whether it is one-tailed or two-tailed
  2. **Type II error (β)** considered tolerable
  3. **Minimum odds ratio** to be detected
  4. **Prevalence of the exposure in the un-diseased control group**
  5. **Ratio of un-diseased controls to diseased study subjects**

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- **In a case–control study**
  - one selects subjects based on the **presence or absence of the disease of interest**,
  - and then investigates the **prevalence of the exposure of interest in each study group.**
- This is in contrast to a cohort study,
  - in which one selects subjects based on the presence or absence of an exposure,
  - and then studies **whether or not the disease of interest develops in each group.**
- Therefore, the fourth variable to be specified for a case–control study is
  - the **expected prevalence of the exposure in the un-diseased control group**,
  - rather than the incidence of the disease of interest in the unexposed control group of a cohort study.

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Example: Sample Size Formula For Case–control Study

$$N = \frac{1}{(p-V)^2}\left[Z_{1-\alpha}\sqrt{\left(1+\frac{1}{K}\right)U(1-U)} + Z_{(1-\beta)}\sqrt{p(1-p)/K + V(1-V)}\right]^2$$

where R, α, β, $Z_{1-\alpha}$, and $Z_{1-\beta}$ are as above, p is the prevalence of the exposure in the control group, and K is the ratio of undiseased control subjects to diseased cases,

$$U = \frac{p}{K+1}\left[K + \frac{R}{1+p(R-1)}\right]$$

and

$$V = \frac{pR}{1+p(R-1)}$$

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NB. Sample size determinations in cohort and Case–control studies

- Assume one is able to obtain information
  - on each of the five variables that factor into these sample size calculations.
  - But it is unrealistic
- **Four of the variables** are totally **in the control of the investigator**, subject to his or her specification:
  - **α, β, the ratio of control subjects to study subjects, and the minimum relative risk to be detected**.
- Only **one of the variables requires data derived from other sources.**
  - **For cohort studies**,
    - this is the **expected incidence of the disease** in the **unexposed control group.**
  - **For case–control studies,**
    - this is the **expected prevalence of the exposure** in the **un-diseased control group.**

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4.5. Sample size calculations for Case series

- Case series are usually used in pharmacoepidemiology
  - to quantitate better incidence of a particular disease in patients exposed to a newly marketed drug.

Example 1:

- In the “Phase IV” post marketing drug surveillance study conducted for prazosin, the investigators collected a case series of 10 000 newly exposed subjects recruited through the manufacturer’s sales force, to quantitate better the incidence of **first-dose syncope**, which was a well-recognized adverse effect of this drug.

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- **Case series are usually used to determine**
  - **Whether a disease occurs more frequently than some predetermined incidence in exposed patients.**
  - Most often, the predetermined **incidence of interest is zero**
  - And one is looking for any **occurrences of an extremely rare illness.**

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Thank you

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